Managed Care Dossier for Lamictal

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1. Change Summary

The following indicates sections within the *Lamictal* dossier where new clinical data has been added within the last year.

Section 4.2 Dosage Forms, Package Sizes, NDC, and WAC (October 2008)

Section 4.5 Use in Special Populations (July 2008)

• Use During Pregnancy

International Lamotrigine Pregnancy Registry (updated)

North American Antiepileptic Drug (NAAED) Pregnancy Registry (updated)

• Use During Lactation (July 2008)

Lamotrigine in breast milk and nursing infants: determination of exposure (updated)

Section 10.1 Summary of Lelorier et al. and economic impact of generic substitution of lamotrigine publication (March 2009)

Section 10.1 Outcome and Economic Evaluation (July 2008)

• Epilepsy

Adherence and associated outcomes (added)

2. EXECUTIVE SUMMARY

Lamictal, an antiepileptic drug (AED) of the phenyltriazine class, is chemically unrelated to existing AEDs.[1] *Lamictal* is approved for a broad spectrum of ages and seizure types such as adjunctive therapy for partial seizures, generalized seizures of Lennox-Gastaut syndrome, and primary generalized tonic-clonic seizures in patients ≥2 years of age. *Lamictal* is also indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED.

Only *Lamictal* has been proven to extend stability by delaying time to occurrence of both depressive and manic episodes for up to 18 months in adults with bipolar I disorder. In addition, *Lamictal* is associated with a favorable tolerability profile and offers a favorable, linear pharmacokinetic profile with no blood monitoring required. Lamotrigine is not highly protein bound and is not metabolized through cytochrome P450, therefore drug interactions are less likely. The favorable tolerability profile along with the combined clinical evidence makes *Lamictal* a favorable candidate for formulary inclusion.

EFFICACY

- The efficacy of *Lamictal* as adjunctive therapy was established in 3 multicenter, placebo controlled, double blind clinical trials in adults with refractory partial seizures [2] [3] [4] and one trial in children (≥2 years) with refractory partial seizures. [5]
- A multicenter, placebo-controlled, double-blind trial established the efficacy of *Lamictal* in adults and children (≥2 years) with primary generalized tonic-clonic seizures.[6]
- A multicenter, placebo-controlled, double-blind trial established the efficacy of *Lamictal* in children (≥2 years) and adults with the difficult-to-treat generalized seizures of Lennox-Gastaut syndrome. [7]
- In a double-blind, controlled trial, adult patients with partial seizures were successfully converted to monotherapy with *Lamictal* from carbamazepine or phenytoin as the single AED. [8] Further prospective data established the safety of conversion to *Lamictal* as monotherapy from valproate in adults with partial seizures. [9]
- The efficacy of *Lamictal* as monotherapy as maintenance treatment of bipolar I disorder was established in two multicenter, double blind, placebo controlled, 18-month studies in patients with current or recent depression, mania, or hypomania.[10,11] Across both studies, *Lamictal* was associated with statistically significant differences versus placebo on delaying time to intervention for a mood episode and overall survival in study.
- A prospectively defined combined analysis of the two studies revealed a statistically significant benefit for *Lamictal* over placebo in delaying the time to occurrence of both depression and mania. [12] The finding was more robust for depression.

SAFETY

Common adverse events in clinical studies of epilepsy patients receiving *Lamictal* included dizziness, headache, blurred or double vision, lack of coordination, sleepiness, nausea, vomiting, insomnia, and rash.[1]

- The most common adverse events (≥5% and numerically greater than placebo) associated with *Lamictal* during the double-blind phase of the maintenance studies in bipolar disorder were: nausea, insomnia, somnolence, back pain, fatigue, rhinitis, non-serious rash, abdominal pain, dry mouth, constipation, vomiting, exacerbation of cough, and pharyngitis.[1]
- Prescribing information for *Lamictal* contains a boxed warning concerning serious rashes requiring hospitalization and discontinuation of treatment in association with the use of *Lamictal*. For more information, as well as information related to additional warnings and precautions, please see prescribing information for *Lamictal*.

3. DISEASE DESCRIPTION

3.1 Epilepsy

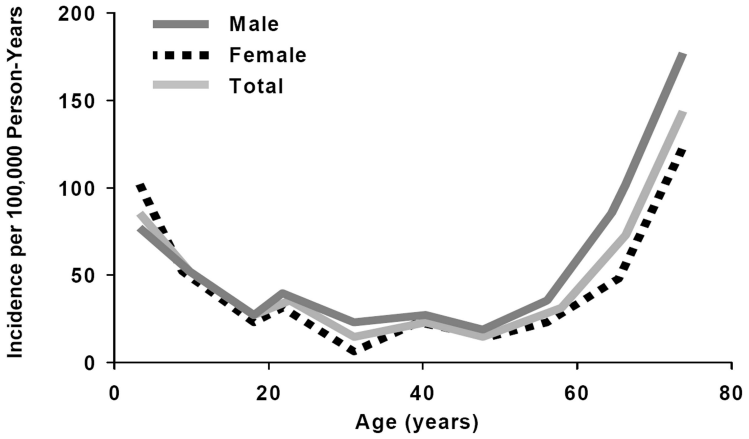
overview of epilepsy

Epilepsy is a chronic neurological disorder characterized by recurrent unprovoked seizures.[13] Typically, epileptic seizures are brief events that occur as a consequence of repeated, spontaneous, transient bursts of abnormal neuronal discharges. Depending on the source and spread of abnormal neuronal activity in the brain, seizures may be expressed as disturbances of behavior, emotion, motor function or sensation.

INCIDENCE AND PREVALENCE

Epilepsy is considered the most common serious neurological disorder.[14,15] The annual incidence of epilepsy in developed countries is estimated to be 50–70 cases per 100,000 of the population. Approximately 2-2.5 million people in the United States have epilepsy.[14,16,17] The incidence of epilepsy is higher in the young (<10 years) and elderly (>60 years) (Figure 1).[18]

Figure 1. Epilepsy Incidence-Rochester Minnesota 1935-1984[18]



pathophysiology

Various abnormalities or dysfunctions associated with epilepsy have been suggested.[19,20,21] Normal brain activity requires a carefully balanced relationship between inhibitory and excitatory activity. Epilepsy may result from a disturbance in the balance between excitatory and inhibitory mechanisms at the neuron level, which results in epileptic seizures when the balance leans toward excitation.

High levels of the excitatory neurotransmitter, glutamate, may account for some types of seizures. Other hypotheses suggest that a shortage of the inhibitory neurotransmitter (GABA) or alterations in ion flux (e.g., sodium and calcium) are associated with certain seizure types.

In approximately 70% of epilepsy cases, the cause is unknown.[14] Etiologies of seizures vary with age: children are more likely to experience epilepsy due to congenital abnormalities and infection, whereas the elderly have a higher incidence of epilepsy due to vascular events such as stroke (Figure 2, Figure 3)

Figure 2. Etiology of Epilepsy in Pediatric Patients Less than 15 Years of Age[14]

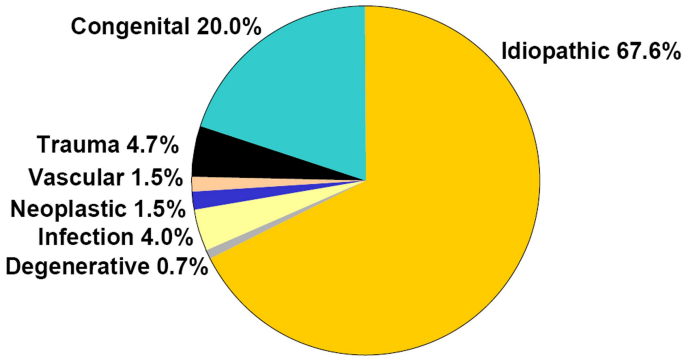
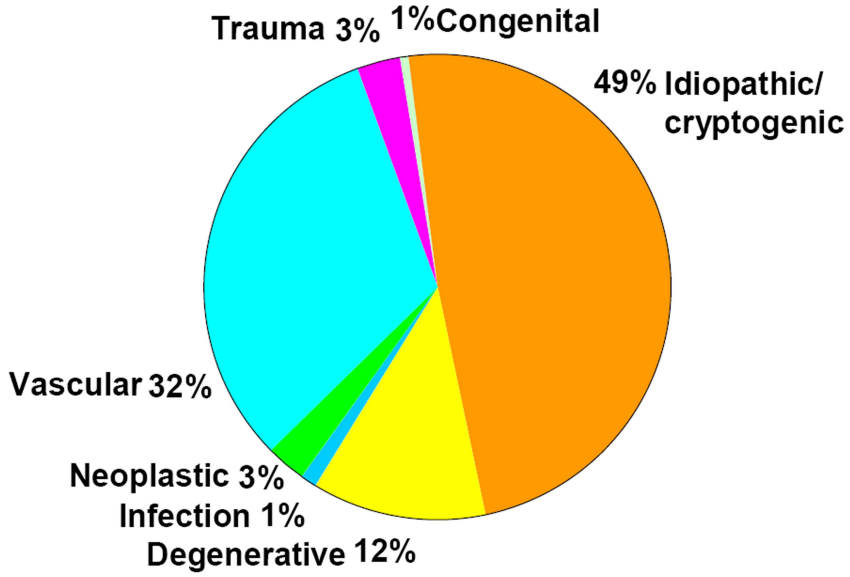


Figure 3. Etiology of Epilepsy in Adults 65 Years of Age and Older[14]



Genetic predisposition plays a role in some types of epilepsy, such as juvenile myoclonic epilepsy.[22] Although the risk of epilepsy can be higher in families with a history of the condition, most cases of epilepsy is not inherited. Some genetic conditions and diseases, such as Tay-Sachs disease, increase the likelihood of acquiring epilepsy. Chromosomal abnormalities such as Down syndrome may also be associated with epilepsy.[23] Specific genes have been found for some particular genetic epilepsies.

Injuries to the brain can produce localized scarring or lesions, which can then be a focus for abnormal electrical activity and produce seizures that affect the parts of the body controlled by the area affected by the lesion.[24]

diagnosis

Seizure events can be elicited by a multitude of external factors (physiological changes, hormonal changes, sleep, sensory stimuli, emotional stress, drugs and drug withdrawal) in otherwise perfectly normal individuals.[19,25] Such single-event cases do not fulfill the diagnostic criteria for epilepsy, which require seizures to be recurrent. The recognition of seizures may be difficult, particularly in young children. However, even in adults there are several conditions that can result in misdiagnosis including: syncope (vasovagal, cardiac), pseudoseizures, panic attacks, migraine, transient ischemic attacks, and narcolepsy.

Finding the cause of seizures is an important part of the assessment of patients with epilepsy, and may impact the patient's prognosis. An accurate initial, or differential diagnosis of epilepsy may depend upon medical and family history, physical and neurological examinations, psychosocial information, and techniques such as x-ray, electroencephalogram (EEG), computerized tomography (CT), and magnetic resonance imaging (MRI).[26]

A diagnosis of epilepsy is primarily made on clinical grounds, and is based on a detailed description of events before, during and after the seizures. Many patients experience impaired consciousness during seizure episodes, therefore an eyewitness account of events is often an essential component of the diagnosis.

The most generally accepted classification for epileptic seizures is that published by the International League Against Epilepsy (ILAE) in 1981 (Table 1).[27] In general, seizures are classified into 2 groups on the basis of whether their onset is partial (focal) or generalized. In addition to the classification of seizures, the ILAE have defined a separate classification for epilepsies and epileptic syndromes (Table 2).

Partial Seizures

Partial seizures are those where clinical and EEG changes indicate a focal point of origin, with a localized spread of electrical discharge limited to within one cerebral hemisphere.[27] Partial seizures can be further classified on the basis of whether or not consciousness is impaired during the attack (Table 1). When consciousness is not impaired, the seizure is classified as a simple partial seizure. When consciousness is impaired, the seizure is classified as a complex partial seizure. Complex partial seizures are the most common type of seizure in adults and most difficult to treat.

Generalized Seizures

Generalized seizures are those in which clinical and EEG changes indicate widespread bilateral involvement from the outset.[27] Consciousness is usually impaired and may represent the initial manifestation of a generalized seizure. Generalized seizures are classified further into individual seizure types on the basis of clinical presentation and EEG changes: tonic-clonic seizures, absence seizures (typical and atypical), myoclonic seizures, clonic seizures, tonic seizures and atonic seizures (Table 1). No known structural abnormalities account for generalized seizures.

Unclassified seizures

Unclassified seizures represent a minority of seizures, which defy classification as partial or generalized.[27]

Table 1. Classification of Seizures[27]

Seizure Type	Locus of Activity	Manifestations	Consciousness	Aura or Warning
Partial Seizures				
Simple Partial	One site or lobe	Approximately 30 seconds Involuntary muscle jerks, e.g., one hand may twitch Sensory (tastes or smells) Psychic or emotional (e.g., fear)	Retain consciousness	Foul smell Metallic taste Lightheadedness Bright light Rising sensation in stomach
Complex Partial	One site or lobe, commonly the temporal lobe	1-3 minutes Automatisms, e.g., pick at clothes, smack lips, wander, repeat words) May begin as a simple partial seizure	Lose consciousness or memory, or may be confused or dazed afterwards	Foul smell Metallic taste Lightheadedness Bright light Rising sensation in stomach
Complex Partial with Secondary Generalization	Locally initiated, then spreads to both hemispheres	(See Generalized Tonic Clonic Seizures below)	Lose consciousness when progresses to generalized seizure	Partial seizure may actually be the "aura" for the generalized seizure
Generalized Seizures				

Seizure Type	Locus of Activity	Manifestations	Consciousness	Aura or Warning
Generalized Tonic-Clonic (formerly Grand Mal)	Both cerebral hemispheres affected from outset	Approximately 2 minutes Muscles rigid (tonic) –Person falls down Rhythmic muscle contractions (clonic) Shallow breathing Incontinence Postictal drowsiness	Lose consciousness	Usually no aura or warning
Absence (formerly Petit Mal)	Both hemispheres	2-15 seconds Staring or blinking Upward rotation of eyes No motor activity Characteristic EEG pattern (Atypical absence seizures may involve automatisms and muscle twitching)	Lose consciousness briefly, but no falling	Usually no aura or warning
Myoclonic	Usually both hemispheres	(Usually occurs in early waking period) Rapid jerks of one or both arms or legs	May or may not lose consciousness	Usually no aura or warning May precede tonic clonic seizure
Atonic (Drop Attacks)	Both hemispheres	10-60 seconds Sudden loss of muscle control (may fall to floor, head drops, jaw slackens) Frequent injuries	Lose consciousness	Usually no aura or warning

Epilepsy Syndromes

Syndromes are defined on the basis of groups of characteristic clinical features relating to seizure type(s), age of onset, EEG abnormality, associated neurological features and family history (Table 2).[28,29,30] Epilepsy syndromes are defined by factors such as:

- Etiology (if known)
- Precipitating factors
- Age of onset
- Characteristic EEG pattern
- Family history

Table 2. Epilepsy Syndromes[28,29,25]

Syndrome	Onset	Description
Primary epilepsies or syndromes		
AED=antiepileptic drug; EEG=electroencephalogram		

Syndrome	Onset	Description
Lennox-Gastaut Syndrome)	Early- to mid-childhood (1 - 8 years)	Associated with brain damage, mental retardation, and developmental disabilities Multiple types of difficult to treat generalized and partial seizures Characteristic EEG pattern Often suffer status epilepticus Seizures may be refractory to AED treatment, so medical control of seizures is often difficult
Childhood Absence Epilepsy/Typical Absence	4 - 8 years old May disappear by adolescence	Are brief but frequent Manifest by clusters of multiple seizures Occasional tonic-clonic seizures may also occur Characteristic and diagnostic EEG Usually controlled on valproate monotherapy
Juvenile Myoclonic Epilepsy	Early adolescence persisting into late adulthood	Tonic-clonic or clonic-tonic-clonic convulsions as well as absence attacks and myoclonic jerks May be inherited Generalized seizures occur most often upon waking in morning Characteristic EEG Responds well to appropriately selected AEDs
Secondary or symptomatic epilepsies or syndromes		
Infantile Spasms/West Syndrome	Typical age range: 2 - 12 months	In many cases, a predisposing factor can be determined, including prenatal and natal factors Characterized by rapid spasms that can occur hundreds of times a day In most cases, associated with mental retardation Medical management is difficult; prognosis is poor
AED=antiepileptic drug; EEG=electroencephalogram		

comorbidities

Epilepsy is associated with comorbidities that affect patient health, and comprehensive management of the patient with epilepsy entails managing these comorbidities as well as gaining control of seizures.(31) Common psychiatric comorbidities of epilepsy include anxiety disorders, major depression, bipolar disorder, and psychosis (interictal and postictal).(32) These comorbidities may occur in patients with epilepsy at a higher incidence than they do in the general population.(33) Depression, a common psychiatric disorder in epilepsy, has a prevalence of 20% - 57% among patients with epilepsy compared with 2% - 4% in the general population.(31) The etiology of depression in epilepsy has not been determined but is thought to be heterogeneous and to include the brain pathology underlying epilepsy, the negative psychosocial impact of epilepsy, and side effects of AEDs.(34) In a U.S. survey, symptoms of bipolar disorder, evident in 12.2% of patients with epilepsy, were 6.6 times more likely to occur compared to a group of healthy adults.(35)

Patients with epilepsy are also at increased risk of cognitive impairment including both memory and learning.(36) Cognitive impairment is attributable to a variety of causes, including adverse neurobiologic effects of seizures or factors unrelated to seizures, such as family or personal psychiatric history.(36,37) (38) Cognitive impairment may also be associated with AEDs.

Many unique challenges are faced by female patients with epilepsy. Challenges may arise from the interactions among epilepsy, endocrine hormones, and AEDs.[39,40,41,42] Special consideration in female patients with epilepsy includes, but is not limited to, menstrual cycle regularity, fertility and ovulatory function, teratogenicity, sexual dysfunction, and bone health.

Approximately 5% of the total yearly visits to the emergency department in patients with epilepsy are related to injuries resulting from seizures.[43] Patients with epilepsy experience mortality rates 2 to 3 times that of the general population. [44] This higher mortality rate may be partly attributable to underlying causes, such as brain tumor or cerebrovascular disease. Collective studies in epilepsy estimate the average rate of suicide is approximately 12% among patients with epilepsy compared to 1.1 - 1.2% in the general population.[45]

IMPACT

Economic Costs

The average treatment-related cost of each new diagnosis of epilepsy in 1995 was: $2,642 during the first 3 months, $329 during year 6, and $6,429 total over 6 years.[46] The high cost at onset is due to diagnosis and initial treatment, then these cost decline partly due to remission and AED discontinuation.

High indirect costs associated with epilepsy arise primarily from decreased productivity attributed to inefficiency at work (including work outside the home and within the household), missed days of work, unemployment, and premature death.[46] The World Health Organization estimated that epilepsy was associated with $12.5 billion in total costs in the U.S. in 2000.[47] Indirect costs incurred by patients with epilepsy who are refractory to AEDs appear to be the primary drivers of the total costs of epilepsy.[48] In a 1995 analysis of the cost of refractory epilepsy in the United States, indirect costs incurred by refractory patients accounted for two thirds to three fourths of total costs, which were $3.9 billion.

PERSONAL COSTS

Epilepsy is associated with significant psychosocial burden.[49] In a study of more than 6000 adults from 10 countries, approximately half reported that they had difficulty accepting their illness.[50] Seventeen percent (17%) of respondents indicated that they felt stigmatized by epilepsy. Factors predictive of stigma included higher seizure frequency, poorer patient knowledge about epilepsy, longer duration of epilepsy, and seizure type. Understanding epilepsy-associated stigmatization and the factors that contribute to it can be important in managing epilepsy.

TREATMENT

Goals

The primary goals of therapy for epilepsy include control of seizures—ideally, achieving freedom from seizures—as well as minimizing the occurrence of adverse events, including those arising from drug-drug interactions, and improving the patient's quality of life. [51] Comorbidities and psychosocial challenges can also affect the clinical course of epilepsy and need to be considered in tailoring treatment strategies to the needs of the individual patient. Although current treatment options can be effective at suppressing acute seizures, no prophylactic treatment is available to prevent the initial development of the condition.

Guidelines

Please refer to the Guidelines for the Treatment of Patients With Epilepsy developed by the American Academy of Neurology (AAN) and American Epilepsy Society (AES) in 2004 and the Expert Consensus Guidelines on the Treatment of Epilepsy from 2005. [51] [52]

3.2 Bipolar Disorder

overview of bipolar disorder

Bipolar disorder, also known as manic-depression, is a medical illness distinguished by marked changes in mood, energy levels, sleep patterns, and behavior. [53] It is defined as the occurrence of episodes of mania or hypomania (abnormal mood elevation, high energy or euphoria) and depression (extreme sadness), often with significant changes in sleep patterns, appetite, and social interaction. Such "mood swings" can

last for hours, days, weeks, or even months. Types of bipolar disorder include: bipolar I disorder, bipolar II disorder, and bipolar disorder not otherwise specified (NOS).

INCIDENCE AND PREVALENCE

It is estimated that over 2 million people in the United States have bipolar disorder. [54] Community studies suggest a lifetime prevalence of bipolar I (0.4 -1.6%) and II disorder (0.5%) of approximately 2% with equivalent distribution between sexes, ethnic groups, and social classes.[53] However, because of the high rate of under diagnosis and misdiagnosis, the actual incidence of bipolar disorder may be even higher.[54] The onset of bipolar disorder typically occurs during late adolescence or early adulthood (before age 20), although it can manifest during childhood or later in life (≥40 years).[55,53] [56]

Although the overall frequency of bipolar disorder appears to be equal between sexes, women may represent a larger portion of those who meet criteria for bipolar II disorder and rapid-cycling.[53] [57] Women with bipolar disorder are more likely to experience an initial episode of depression, whereas men with bipolar disorder are more likely to experience an initial episode of mania.[53]

There is a familial pattern to bipolar disorder.[53] First-degree biological relatives of individual with bipolar I disorder have elevated rates of bipolar I disorder (4-24%) and bipolar II disorder (1-5%). Twin and adoption studies provide strong evidence for a genetic influence. Other studies have also indicated this trend in bipolar II disorder compared with the general population.

PATHOPHYSIOLOGY

The precise pathophysiology of bipolar disorder remains unclear.[58] While several theories exist, no single unified hypothesis explains the pathophysiology of bipolar disorder. One or more of the following hypotheses may explain the pathophysiology of bipolar disorder:

- Anatomical abnormalities of the brain
- Biochemical changes
- Genetic component
- Neurotransmitter-related alterations
- Physiological abnormalities
- Sleep and biological rhythm disturbances

diagnosis

Mania, Hypomania and Mixed Episodes

Mania is a distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting ≥1 week. [53] Hypomania is a distinct period of abnormally and persistently elevated, expansive, or irritable mood lasting ≥4 days. Both manic and hypomanic episodes involve abnormal elevation in mood along with ≥3 additional symptoms of:

- Inflated self-esteem or grandiosity
- Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
- Pressure of speech (more talkative than usual or pressure to keep talking)
- Flight of ideas or subjective experience that thoughts are racing
- Distractibility (i.e., attention too easily drawn to unimportant or irrelevant stimuli)
- Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitiation
- Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)

A comparison of the features of mania and hypomania are shown in Table 3.

Table 3. Comparison of Mania and Hypomania

	Mania	Hypomania
Mood	Abnormally elevated, irritable, or expansive mood	Abnormally elevated, irritable, or expansive mood, but to a lesser degree than in mania
Hospitalization	Typically required	Not required
Functioning (social/occupational)	Impaired	Not required
Intensity	Causes marked impairment	No marked impairment
Duration	≥7 days	≥4 days
Important features	Psychotic symptoms often present; patients often feel agitated	Psychotic symptoms rare; patients feel productive and energetic; they may not perceive a problem and, hence, not seek care

Mania is typically divided into 2 subgroups: classic and mixed.[53] In classic mania, the patient only exhibits symptoms characteristic of mania. In a mixed state, the patient exhibits, concurrently, symptoms characteristic of mania and symptoms characteristic of depression nearly every day for ≥1 week. During a mixed episode, the individual experiences rapidly alternating moods (sadness, irritability, euphoria) accompanied by symptoms characteristic of a manic episode. Diagnostic criteria for a mixed-state episode include:

• Meeting diagnostic criteria for both a manic and a depressive episode

• Having severe enough mood disturbance to either: cause marked impairment in one's occupational functioning or one's usual social activities or relationships with others, necessitate hospitalization in order to prevent harm to self or others, or display psychotic features

Depressive Episodes

Depression is a mood abnormality that includes depressed mood or loss of interest or pleasure in usually pleasurable activities.[53] The essential feature of a major depressive episode is a period of ≥2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities. In addition, major depressive disorder is classified as having ≥5 of the following symptoms occurring within the same 2-week period:

• Significant weight loss when not dieting, or weight gain, or decrease in appetite nearly every day

• Insomnia or hypersomnia (decreased or increased sleep)

• Psychomotor retardation or agitation (decreased or increased movement)

• Fatigue or loss of energy nearly every day

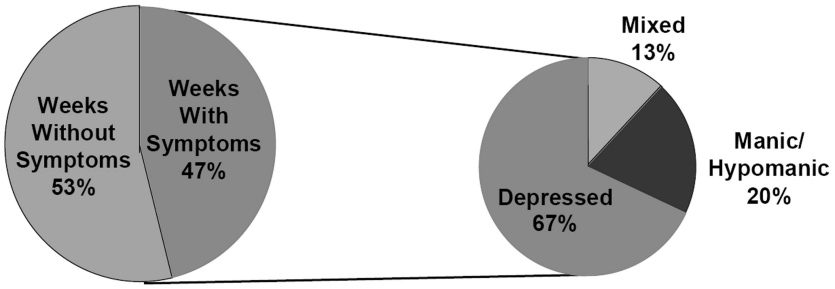
• Feelings of worthlessness or excessive or inappropriate guilt (may be delusional) nearly every day

• Diminished ability to think or concentrate, or indecisiveness nearly every day

• Recurrent thoughts of death (not just fear of dying), or suicidal ideation (thoughts of committing suicide) without a specific plan, or a suicide attempt or a specific plan for committing suicide

In a prospective, natural history study of patients with bipolar I disorder with a mean follow-up of 12.8 years, patients spent nearly half of their time symptomatically ill (Figure 4).[59] Total weeks spent symptomatically depressed exceeded weeks spent manic by a factor of 3.

Figure 4. Proportion of Total Weeks Spent Symptomatically Ill in Bipolar I Disorder and Proportion of Symptom Type Among Ill Patients



Types of Bipolar Disorder

The four main categories of bipolar disorder are:[53]

• Bipolar I disorder: characterized by the occurrence of ≥1 manic episodes or mixed episodes (daily episodes of mania and depression for 1 week). Individuals often have 1 major depressive episodes.

• Bipolar II disorder: characterized by the occurrence of ≥1 major depressive episodes along with ≥1 episode of hypomania

• Bipolar disorder NOS: characterized by bipolar features that do not meet criteria for any specific bipolar disorder

• Cyclothymic disorder: chronic, fluctuating mood disturbance involving numerous periods of hypomanic symptoms and numerous periods of depressive symptoms that do not meet full criteria for hypomanic or major depressive episodes over ≥2 years (1 year in children and adolescents). During this period, the person must not have been symptom-free for ≥2 months at a time, and they cannot have any episode of major depression, hypomania, mania, or mixed episodes during the first 2 years of the disturbance. There is a 15% to 50% risk that individuals with cyclothymia may go on to meet diagnostic criteria for bipolar disorder.

Rapid-Cycling

The specifier of rapid-cycling is a clinically recognized subtype of bipolar disorder characterized by the occurrence of ≥4 mood episodes in a 12-month period.[53] Such episodes often occur in a random pattern rather than in a distinct cycle. The episodes must be marked either by a period of partial or full remission for ≥2 months or by a switch to an episode of the opposite polarity. Rapid-cycling bipolar disorder is often transient and difficult to treat, and it appears to predict a poor prognosis over the short-term. Approximately 5-15% of patients with bipolar disorder experience rapid-cycling. Women represent 70-90% of patients with rapid-cycling bipolar disorder.

COMORBIDITIES

Substance abuse and panic disorder are common comorbidities in patients with bipolar disorder. [60,61,62] These illnesses can confound an accurate diagnosis of bipolar disorder and have the potential to negatively affect prognosis.[58]

MISDIAGNOSIS

Misdiagnosis remains a major treatment challenge of bipolar disorder. According to a survey by the National Depressive and Manic-Depressive Association (NDMDA, now known as the Depression and Bipolar Support Alliance [DBSA]) in 2000, 69% of patients with bipolar disorder were misdiagnosed, compared with 73% in the 1992 survey.[54,63] Common misdiagnoses included unipolar depression and anxiety disorder (Table 4).

Table 4. NDMDA Survey from 2000: Most Common Misdiagnoses (N = 600)[54]

Misdiagnosis	% of Patients Reporting
Unipolar depression	60%
Anxiety disorder	26%
Schizophrenia	18%
Borderline personality disorder	17%
Alcohol/substance abuse	14%
Schizoaffective disorder	11%

Significantly more women than men were misdiagnosed (72% vs 62%, respectively), and patients consulted an average of 4 physicians before receiving an accurate diagnosis.[54,63] Individuals were more likely to report depressive versus manic symptoms, contributing to the frequent misdiagnosis of major depressive disorder.

Clinicians may want to consider incorporating validated screening tools, such as the Mood Disorder Questionnaire (MDQ).[64] The MDQ has 13 self-rated questions and help detect symptoms of bipolar disorder. In a validation study, 7 of 10 patients with bipolar disorder were identified correctly, and 9 of 10 patients without bipolar disorder were excluded from this diagnosis. When used in combination with longitudinal and cross-sectional analyses, as well as with family histories, diagnostic surveys can provide additional insight into predicting a bipolar course of illness.[65,66]

Discrimination between bipolar depression and unipolar depression is important for treatment choices. Antidepressants, including tricyclic antidepressants, selective-serotonin reuptake inhibitors, monoamine oxidase inhibitors, and atypical antidepressants, have been reported to increase the incidence of switch to mania or hypomania in patients with bipolar disorder. [67,68,69] However, conflicting evidence exists in this area. [67] [70,71] The true incidence of affective switch is controversial due to the underlying nature of the disease and lack of many randomized, placebo-controlled, clinical trials of treatment with antidepressants in bipolar disorder.

Stang et al evaluated the time to diagnosis of bipolar disorder, as well as cost of delayed diagnosis, in 1084 patients with bipolar disorder identified from a large U.S. managed care database and 5420 case controls. The median time to between initial mental health diagnosis and diagnosis of bipolar disorder was 21 months with 33% of patients receiving a diagnosis of bipolar disorder in <6 months and the remaining 47% diagnosed in ≥4 years. The number and duration of antidepressant therapy increased as time to diagnosis of bipolar disorder increased; 23% of patients with bipolar disorder with a ≥4-year lag from initial mental health diagnosis to diagnosis of bipolar disorder received ≥4 different antidepressants during that time period and spent 21.1% of their pre-diagnosis time receiving antidepressants.[72] In the comparison group, 1% of those followed for ≥4 years before the index date received ≥4 antidepressants, spending 2.2% of pre-index time receiving antidepressants.

impact

Suicide

Patients with bipolar disorder are more likely to attempt or complete suicide than the general population, patients unipolar depression or patients with other mental illness.[58] [73,74,75] [76] The lifetime risk of ≥1 suicide attempt ranges from 25% to 50% among patients with bipolar disorder. Nearly one in five patients with bipolar disorder commits suicide. Most suicides occur during the depressed phase.

Economic Costs

In 1990, the World Health Organization, identified bipolar disorder as the sixth leading cause of disability-adjusted life years in the world among people aged 15-44 years. [77] Bipolar disorder is ranked as one of the most costly mental health conditions. [78] [79] In 1998, the direct and indirect lifetime medical costs related to bipolar disorder were estimated at $24 billion.[80] In a study of patients insured through a large staff-model health maintenance organization, healthcare costs for patients with bipolar disorder exceeded those for patients treated for major depression. [81] These costs were driven by disproportionately high use of specialty mental health services, substance abuse treatment, and inpatient care. In another review of expenditures from employer-sponsored insurance claims in 1996, the hospital admission rate for patients with bipolar disorder was 39.1% compared with 4.5% for all other behavioral health claimants. [79]

An average of $2470 per patient per year was paid by insurance plans for patients with bipolar disorder, a full 400% more, on average, than for all other behavioral healthcare claimants.

Employment

A substantial number of respondents (88%) to the NDMDA survey in 2000 believed that bipolar disorder, when not managed effectively, affected their ability to perform job duties (Table 5).[63] In addition, >60% of respondents changed jobs more often than their peers, completely changed careers, or believed that they were treated differently from other employees.

Table 5. NDMDA Survey in 2000: Overall Impact Of Symptoms On Employment When Illness Is Not Effectively Managed (N = 600)[63]

Statements about employment	Percent agreement with statement
Illness affected abilities to perform job duties	88%*
Changed jobs more frequently than peers	65%*
Completely changed careers/professions	60%
Treated differently from other employees	63%*
Quit working outside the home	58%*
Passed up for a promotion	65%*
Given decreased job responsibilities	48%*
*Significantly higher than 1992 survey results at 95% confidence level.	

Personal Costs

Like other forms of mental illness, bipolar disorder deeply impacts one's ability to think, feel, and act and can have profound personal consequences. For example, when properly treated, patients with bipolar disorder are less likely to engage in alcohol/substance abuse or to develop financial difficulties; however, when untreated, the incidence of such events increases considerably (Table 6).[54].

Table 6. NDMDA Survey in 2000: Impact Of Bipolar Disorder On Personal Events (N = 600)[54]

	Without Treatment	With Treatment
Unstable relationships	68%	53%
Spending sprees	52%	37%
Financial difficulty/bankruptcy	51%	43%
Physical health problems	46%	48%
Sexual promiscuity	43%	18%
Alcohol/substance abuse	37%	14%
Fired from job	37%	21%
Injured self/others	35%	23%

TREATMENT

Goals

Treatment of bipolar disorder should include both 1) managing acute episodes, where the primary goal is to achieve remission and 2) maintenance, where the primary goal is to prevent or delay the recurrence of mood episodes. [82] Goals of management of bipolar disorder also include establishing and maintaining a therapeutic alliance, monitoring psychiatric status, providing patient education, enhancing patient compliance, promoting patterns of regular sleep, anticipating patient stressors, identifying new episodes early, and minimizing functional impairments.

Guidelines

Please refer to the American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Bipolar Disorder from 2002 and the Expert Consensus Guidelines for the Treatment of Bipolar Disorder from 2004. [82,83]

4. PRODUCT DESCRIPTION

4.1 Generic Name, Brand Name and Therapeutic Class

a. **Generic Name**: lamotrigine

b. **Brand Name**: Lamictal®

c. **Therapeutic Class**: an antiepileptic drug (AED) of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs

4.2 Dosage Forms, Package Sizes, NDC, and WAC

Table 7. *Lamictal* Chewable Dispersible Tablets

Dosage Strength	Description	Package Size	NDC #	Average Wholesale Price (03/05/2009)	Wholesale Acquistion Costs (03/05/2009)
2 mg	White to off-white, round tablets debossed with "LTG" over "2"	Bottles of 30	0173-0699-00 Order directly from GlaxoSmithKline 1-800-334-4153	Not applicable	Not applicable
5 mg	White to off-white, caplet-shaped tablets debossed with "GX CL2"	Bottles of 100	NDC 0173-0526-00	$513.89	$411.11
25 mg	White, super elliptical-shaped tablets debossed with "GX CL5"	Bottles of 100	NDC 0173-0527-00	$551.68	$441.34
Average Wholesale Price (AWP) is a price calculated and reported by Wolters Kluwer Health Inc., First DataBank Inc and other third party data vendors. AWP does not represent a price at which GSK sells this product. Wholesale Acquisition Cost (WAC) is the listed price to wholesalers and warehousing chains, not including prompt pay, stocking or distribution allowances, or other discounts, rebates, or chargebacks. Listed price may not represent prices charged to other customers, including specialty distributors.					

Table 8. *Lamictal* Tablets

Dosage Strength	Description	Package Size	NDC#	Average Wholesale Price (03/05/2009)	Wholesale Acquistion Costs (03/05/2009)
25 mg	White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25"	Bottles of 100	NDC 0173-0633-02	$531.09	$424.87
100 mg	Peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100"	Bottles of 100	NDC 0173-0642-55	$606.64	$485.31
Average Wholesale Price (AWP) is a price calculated and reported by Wolters Kluwer Health Inc., First DataBank Inc and other third party data vendors. AWP does not represent a price at which GSK sells this product. Wholesale Acquisition Cost (WAC) is the listed price to wholesalers and warehousing chains, not including prompt pay, stocking or distribution allowances, or other discounts, rebates, or chargebacks. Listed price may not represent prices charged to other customers, including specialty distributors.					

Dosage Strength	Description	Package Size	NDC#	Average Wholesale Price (03/05/ 2009)	Wholesale Acquistion Costs (03/05/ 2009)
150 mg	Cream, scored, shield-shaped tablets debossed with "LAMICTAL" and "150"	Bottles of 60	NDC 0173-0643-60	$398.93	$319.14
200 mg	Blue, scored, shield-shaped tablets debossed with "LAMICTAL" and "200"	Bottles of 60	NDC 0173-0644-60	$434.29	$347.43
Lamictal Starter Kit for Patients **Taking** valproate; contains 25 mg tablets	White, scored, shield-shaped tablets debossed with "LAMICTAL" AND "25"	Blister-pack of 35 tablets	NDC 0173-0633-10	$185.88	$148.70
Average Wholesale Price (AWP) is a price calculated and reported by Wolters Kluwer Health Inc., First DataBank Inc and other third party data vendors. AWP does not represent a price at which GSK sells this product. Wholesale Acquisition Cost (WAC) is the listed price to wholesalers and warehousing chains, not including prompt pay, stocking or distribution allowances, or other discounts, rebates, or chargebacks. Listed price may not represent prices charged to other customers, including specialty distributors.					

Dosage Strength	Description	Package Size	NDC#	Average Wholesale Price (03/05/2009)	Wholesale Acquistion Costs (03/05/2009)
Lamictal Starter Kit for Patients **Taking** carbamazepine, phenytoin, phenobarbital, primidone, or rifampin and **Not Taking** valproate; contains 25 mg and 100 mg tablets	White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" Peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100"	Blisterpack of 84, 25- mg tablets and 14, 100 mg tablets	NDC 0173-0594-01	$531.04	$424.83
Lamictal Starter Kit for Patients **Not Taking** carbamazepine, phenytoin, phenobarbital, primidone, rifampin, or valporate; contains 25 mg and 100 mg tablets	White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" Peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100"	Blisterpack of 42, 25-mg tablets and 7, 100-mg tablets	NDC 0173-0594-02	$265.53	$212.42
Average Wholesale Price (AWP) is a price calculated and reported by Wolters Kluwer Health Inc., First DataBank Inc and other third party data vendors. AWP does not represent a price at which GSK sells this product. Wholesale Acquisition Cost (WAC) is the listed price to wholesalers and warehousing chains, not including prompt pay, stocking or distribution allowances, or other discounts, rebates, or chargebacks. Listed price may not represent prices charged to other customers, including specialty distributors.					

DPS/AHFS Drug Classification: 28:12.92 Miscellaneous Anticonvulsants

4.3 AHFS or Other Drug Classification

DPS/AHFS Drug Classification: 28:12.92 Miscellaneous Anticonvulsants

4.4 FDA Approved Indications

FDA Approved Indications/ FDA Approval Dates:

• *Lamictal* is indicated as adjunctive therapy for partial seizures (12/27/94), the generalized seizures of Lennox Gastaut syndrome (8/24/98), and Primary Generalized Tonic-Clonic seizures (9/22/06) in adults.

• *Lamictal* is indicated as adjunctive therapy for partial seizures (1/10/03), the generalized seizures of Lennox Gastaut syndrome (8/24/98), and Primary Generalized Tonic-Clonic seizures (9/22/06) in pediatric patients (2 years of age).

• *Lamictal* is indicated for conversion to monotherapy in adults with partial seizures who are receiving treatment with a carbamazepine (CBZ), phenytoin (PHT), phenobarbital (PB), primidone (PM), or valproate (VPA) (12/16/98) or valproate (01/14/04) as the single antiepileptic drug (AED).

• Safety and effectiveness of *Lamictal* have not been established 1) as initial monotherapy, 2) for conversion to monotherapy from AEDs other than CBZ, PHT, PB, PM, or VPA, or 3) for simultaneous conversion to monotherapy from 2 concomitant AEDs.

• *Lamictal* is indicated for the maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy (06/20/03).

•The effectiveness of *Lamictal* in the acute treatment of mood episodes has not been established.

4.5 Use in Special Populations

Refer to Enclosed Prescribing Information.

Use During Pregnancy

background

The average frequency of birth defects in women with epilepsy using AED monotherapy ranges between 3.3% and 4.5% as compared with a range of 1.6 to 2.7% in the general population depending on the malformation classification system and follow-up after birth. (84) (85) (86) (87,88) (89)

Product label information

Lamictal has a FDA Pregnancy Category C designation.(90) There are no adequate and well-controlled studies of pregnant women receiving *Lamictal*. *Lamictal* should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

clinical information

Although lamotrigine was not found to be teratogenic in animal studies of mice, rats, or rabbits, lamotrigine decreased fetal folate concentrations in rats, an effect known to be associated with teratogenesis in animals and humans.(90)

Pregnancy registries

Note that these findings should be interpreted with caution since these registry studies are still ongoing and because the sizes of these registries are insufficient to permit definitive conclusions regarding the safety of lamotrigine in pregnant women and their developing fetuses.

Registries are not designed to monitor the risk associated with specific malformations. However, the registries can generate signals for specific malformations which are further investigated by either assessing other registry information or by follow-up studies designed specifically for that aim.

International Lamotrigine Pregnancy Registry

Since 1992, GlaxoSmithKline has managed a pregnancy registry as part of an ongoing program in epidemiologic safety monitoring. (91,92) The Registry is intended to supplement animal toxicology data and

to assist clinicians in weighing the risks and benefits of treatment for individual patients. To facilitate monitoring fetal outcomes of pregnant women exposed to *Lamictal Tablets*, physicians are encouraged to register patients before fetal outcome (e.g., ultrasound, results of amniocentesis, birth, etc.) is known. Physicians can obtain information by contacting the Lamotrigine Pregnancy Registry at (800) 336-2176. The Interim Report of the Lamotrigine Pregnancy Registry through September 30, 2008 is enclosed for review.

In this Registry, pregnancy-outcome ascertainment is obtained through subsequent follow-up with the reporting physician. The Registry is sponsored by GlaxoSmithKline considering the advice of the Center for Disease Control, a United States (US)-based institution, neurology, and teratology specialists. These individuals provide independent review of the data as members of the Advisory Committee for the Registry. The percentage with major birth defects in pregnancies with known birth defect status was calculated for lamotrigine monotherapy and for polytherapy stratified by trimester of exposure. The Registry collects information on exposures to *Lamictal Tablets* for all therapeutic uses.

As of September 30, 2008, there were 3212 prospectively registered pregnancies with 243 pending the pregnancy outcome and 825 lost to follow-up.[92] Of the remaining cases, 2144 pregnancy reports are closed with 2183 known outcomes. The following outcomes exclude spontaneous pregnancy losses, fetal deaths, and induced abortions not involving major defects.

Lamotrigine Monotherapy: In the reports with first trimester lamotrigine exposure as monotherapy, 33 major birth defects were reported among 1337 outcomes (Table 9). The observed proportion of births with major defects is 2.5% (95% Confidence Interval [CI]: 1.7%-3.5%) involving first trimester monotherapy exposure.

In prospective reports of lamotrigine monotherapy exposure in the second trimester, there were 4 major birth defects reported in 75 outcomes. One major birth defect was reported in 18 outcomes with third trimester lamotrigine monotherapy exposure.

Table 9. Prospective Registry from September 1, 1992 through September 30, 2008 – Lamotrigine Monotherapy Exposure in Pregnancy by Earliest Trimester of Exposure and Outcome [92]

Earliest Trimester of Exposure	Major Birth Defects			No Major Birth Defects Reported*			Spontaneous Pregnancy Loss †,‖	Total Outcomes §
	Live Birth	Fetal Death ‡	Induced Abortion	Live Birth	Fetal Death ‡	Induced Abortion		
First	29	1	3	1304	7	31	82	1457
Second	4	0	0	71	0	0	0	75
Third	1	0	0	17	0	0	0	18
Unspecified	0	0	0	5	0	0	0	5
Total	34	1	3	1397	7	31	82	1555

*Birth defect not reported but cannot be ruled out; †Pregnancy loss occurring <20 weeks gestation; ‡Pregnancy loss occurring ≥20 weeks gestation; §Totals include 28 sets of twins and 1 set of triplets; ‖Includes defect and non-defect reports. Due to the likelihood of misclassification bias, spontaneous pregnancy losses <20 weeks gestation are excluded from the calculation of the risk of birth defects.

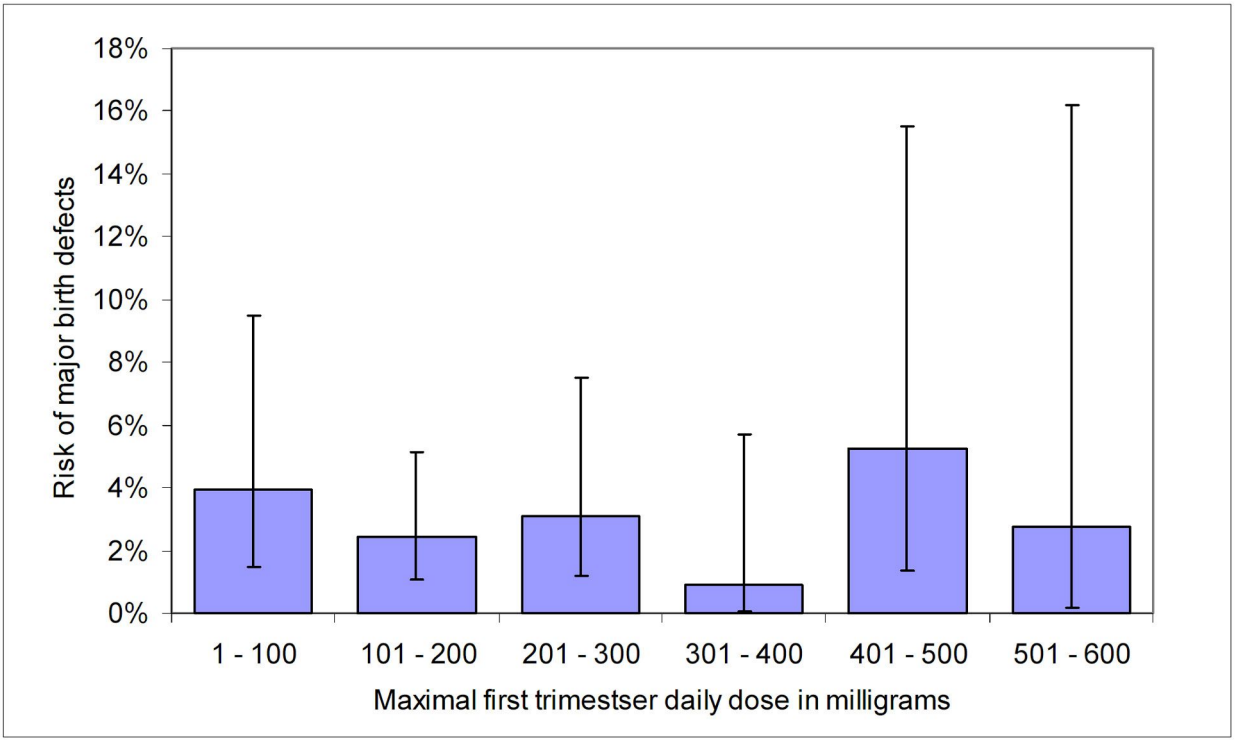
Polytherapy including Valproate (VPA): In the reports with first trimester exposure to polytherapy including VPA (with or without one or more additional AEDs), there were 16 major birth defects reported among 146 outcomes. The observed proportion of births with major defects is 11% (95% CI: 6.6%-17.5%).[92]

Polytherapy not including Valproate: In the reports with first trimester exposure to polytherapy not including VPA, there were 9 major birth defects reported in 392 outcomes. The observed proportion of births with major defects is 2.3% (95% CI: 1.1%-4.5%).

Figure 5 summarizes the risk of major birth defects in the Registry by dosing category using the maximum dose of *Lamictal Tablets*, as monotherapy, in the first trimester through March 31, 2006.[93] Mean and median maximal first trimester maternal doses of *Lamictal Tablets* for infants with major birth defects, respectively, were 248.3 mg/day (d) and 200 mg/d; the mean and median doses for infants without defects were 278.9 mg/d and 200 mg/d, respectively. There was no evidence of a dose-effect, up to 400 mg/d, on

the frequency of major birth defects. There are not sufficient data above 400 mg/d to establish or refute the occurrence of a dosing effect for lamotrigine monotherapy at these doses. The highest first trimester monotherapy dose of *Lamictal Tablets* was 1,200 mg/day. [92,93]

Figure 5. Risk of Major Birth Defects by Maximal First Trimester Monotherapy Dose of *Lamictal* through March 31, 2006 [93]



The Registry has not detected evidence of an appreciable increase in the overall risk of major birth defects.[92] Assuming a minimum baseline risk of major defects in women with treated epilepsy of 2-3%, the current sample size of 1261 first trimester monotherapy exposures is sufficient to detect, with 80% power, a 1.44 to 1.54-fold increase over baseline in the overall rate of birth defects. However, the lamotrigine monotherapy sample size, to date, remains too small for formal comparisons of the rates of specific birth defects.

United Kingdom Epilepsy and Pregnancy Registry

Since December 1996, Morrow et al has managed an ongoing prospective, observational, registration and follow-up study of pregnancy exposures in women with epilepsy in the United Kingdom (UK). [94] Women with epilepsy who become pregnant who are referred before the pregnancy outcome is known, whether or not they are receiving an AED (monotherapy or polytherapy), are eligible for inclusion. Cases are referred by patients themselves, neurologists, specialist epilepsy nurses, obstetricians, midwives, and general practitioners and other health care professionals. Outcome data is collected 3 months following delivery by sending a standardized questionnaire to the patient's general practitioner.

As of March 31, 2005, the UK Epilepsy and Pregnancy Registry has registered 4414 pregnancies and collected full outcome data on 3607 (82%) cases. Of the remaining exposures, 8.1% were lost to follow-up. The overall major congenital malformation rate for all AED exposed cases was 4.2% (95% CI 3.6%-5%). The rate for women with epilepsy who had not taken AEDs during pregnancy was 3.5% (95% CI 1.8%-6.8%). The rate was significantly higher in polytherapy (6%; 95% CI 4.5%-8%) compared to monotherapy (3.7%; 95% CI 3%-4.5%) exposures ($P = 0.010$). The major congenital malformation (MCM) rate of *Lamictal Tablets* and VPA in combination (n = 141) was 9.6% (95% CI 5.7%-15.7%). The overall rate with Lamictal Tablets (n = 647) as monotherapy was 3.2% (95% CI 2.1%- 4.9%) although a positive dose response for MCMs was noted for *Lamictal Tablets* as monotherapy (Table 10). The mean

daily dose of *Lamictal Tablets* was significantly higher for those with a MCM compared with those without a MCM respectively (352.4 mg/d and 250.6 mg/d; $P = 0.005$).

Table 10. Major Congenital Malformation rate by Monotherapy Dose Category of *Lamictal Tablets* through March 31, 2005 [94]

Maximum Daily Dose of *Lamictal Tablets* (mg/day)	Major Congenital Malformations/ Total Informative Exposures	Rate (%)	95% Confidence Interval
<100	2/151	1.3	0.4 - 4.7
100–200	4/208	1.9	0.8 - 4.8
>200	15/279	5.4	3.3 - 8.7

North American Antiepileptic Drug (NAAED) Pregnancy Registry

The NAAED Pregnancy Registry is an ongoing registry established in 1997 for pregnant women in the US and Canada receiving AEDs for any medical condition.[92] Patients can enroll themselves in the NAAED Pregnancy Registry by calling (888) 233-2334. Infants are examined 4-8 weeks following delivery. The NAAED Pregnancy Registry defines major malformations as structural abnormalities with surgical, medical, or cosmetic importance identified between birth and 5 days.[95]

As of March 1, 2006, the NAAED Pregnancy Registry has registered 684 infants born to women receiving *Lamictal Tablets* as monotherapy in the first trimester of pregnancy, including livebirths, stillbirths, and elective terminations for anomalies. The overall major malformation rate was 2.3% (16/684; 95% CI 1.3-3.8%) for *Lamictal Tablets* as monotherapy during the first trimester compared with 1.62% (CI 1.0-2.7%) in an unexposed comparison group (the Brigham and Women's Hospital [BWH] birth malformations surveillance program in Boston, Massachusetts).

Five of the 684 infants exposed to *Lamictal Tablets* had non-syndromic oral clefts (7.3 per 1,000; 3 isolated cleft palate, 1 isolated cleft lip, 1 bilateral cleft lip and palate) in comparison with a prevalence rate of 0.7 per 1,000 in the unexposed comparison group of the NAAED Pregnancy Registry; this represents a 10-fold increase in the frequency of non-syndromic oral clefts.[95] A prevalence rate of 2.5/1,000 (2 cleft palate, 2 cleft lip and palate) was reported among 1,623 infants exposed to lamotrigine as monotherapy who had enrolled in five other registries (GSK International Lamotrigine Registry, UK Epilepsy and Pregnancy Register, Swedish Medical Birth Registry, Australian Pregnancy Registry, and the Danish Multicentre Registry).

European Registry of Antiepileptic Drugs in Pregnancy (EURAP)

EURAP is an ongoing prospective multi-country AED registry that aims to evaluate the comparative risk of major malformations in infants exposed to different AED monotherapy and polytherapy combinations for any indication during pregnancy.[92,96] Follow-up data are collected up to one year after delivery. EURAP was established in 1999 as the European central registry of AED use in pregnancy, but has since expanded to include countries in Asia, Oceania, and South America. EURAP will not release full major malformation data relating to all AEDs until a set number of prospective pregnancies has been enrolled (n = 5000). As of May 2007, 4,427 prospective pregnancies had completed the 1 year follow-up. Of these pregnancies, 3,512 (80%) were taking AED monotherapy, 753 (17.1%) were taking 2 AEDs and 128 (2.9%) were taking ≥ 3 AEDs. The most frequently used AEDs as monotherapy were CBZ (n = 1205), VPA (n = 836), *Lamictal Tablets* (n = 812) and phenobarbital (PB, n = 212). Among prospective pregnancies with first trimester exposure, the malformation rate was 5.6% with AED monotherapy and 9% with AED polytherapy. Based on data through January 2004 in 1,956 pregnancies of 1,882 women with epilepsy, *Lamictal Tablets* as monotherapy was associated with an increased pill burden or dosage when evaluated by multivariate analysis (n = 238; OR: 3.8 [2.1-6.9]).[97] Several registries presented data in addition to its inclusion within EURAP and are summarized below.

An Australia-wide, prospective, voluntary, telephone-interview-based, observational registry was established in 1999.[92,98] The registry enrolled three groups of women: those with epilepsy taking AEDs, untreated women with epilepsy, and those taking AEDs for a nonepileptic indication. Follow-up telephone interviews are conducted up to 12 months after delivery. As of December 31, 2004, 810 women were enrolled (86% enrolled prospectively) with 737 birth outcomes comprising 657 live births without defects;

40 were live births with defects (11 detected within first year after birth), 9 were induced abortions for defects, 23 were spontaneous abortions, and 7 were stillbirths. The reason for AED treatment was predominantly partial (49%) and generalized (45%) epilepsy. In women exposed to *Lamictal Tablets* as monotherapy, the incidence of birth defects was approximately 5% (6/102) which was not statistically significantly greater than the rate in women not exposed to medication during pregnancy (3.3%). In women exposed to *Lamictal Tablets* as polytherapy, the incidence of birth defects was 6.6% (6/91). An analyses of the Australian Registry did not demonstrate a statistically significant dose-response for major congenital malformations associated with *Lamictal Tablets*. The mean daily dose of *Lamictal Tablets* as monotherapy was 367 mg for those with birth defects compared to 278 mg for those without birth defects.

Results from a prospective pregnancy registry in Denmark (n = 147) were reported prior to entering EURAP.[92] [99] This registry included 51 (35%) women with epilepsy who received *Lamictal Tablets* (monotherapy and polytherapy) during pregnancy (mean dose 385 mg/d) from September 1996 to May 2000. Folic acid supplementation was used by 80% of patients in the first trimester. The overall risk of malformations among newborns in the AED-exposed group was 3.1%. The risk of malformations in patients receiving *Lamictal Tablets* was 2.0%. One woman receiving combination *Lamictal Tablets* (150 mg daily) and oxcarbazepine (2400 mg daily) and 5 mg/day of folic acid supplementation during the first trimester, gave birth to an infant with a significant congenital malformation (ventricular septal defect).

As part of the EURAP project in Germany, Gaus et al compared seizure frequency and dose modification during the first, second, and third trimesters of pregnancy in women receiving AEDs (including *Lamictal Tablets*, n = 63) as monotherapy.[100] In the first, second, and third trimesters respectively, 17%, 19%, and 14% of patients receiving *Lamictal Tablets* experienced increased seizures. Dose modifications were performed in 68% of patients receiving *Lamictal Tablets* during pregnancy. Reasons for dose modifications were recurrent seizures (59%), low serum levels (60%), and fear of malformations (4%). As of January 2007, Coban et al reported 810 cases (793 prospectively, 89%) in Germany with 489 live births, 33 spontaneous abortions, 16 induced abortions, 4 stillbirths, and 5 perinatal deaths.[101] Based on 25 major congenital malformations, the malformation rate was 3.6% with AEDs as monotherapy and 5.7% as polytherapy. Four more cases are not yet classified. *Lamictal Tablets* was the most frequently used AED as monotherapy (43.2%). The major malformation rate with *Lamictal Tablets* was 3.8% (n = 6).

Swedish Medical Birth Registry

The Swedish Medical Birth Registry was established in 1973 and collects data on nearly all births (>95%) in Sweden.[92,102,103] Information on the women's pregnancy is collected prospectively by the attending midwife or physician starting with an interview at the first antenatal visit at 10-12 weeks. Malformations are recorded descriptively and there is no differentiation of major and minor malformations. Between 1995 and 2006, 403 monotherapy exposures and 133 polytherapy exposures with *Lamictal Tablets* have been reported to the registry. In infants exposed *in utero* to monotherapy with *Lamictal Tablets*, there were 18 reported malformations providing a risk of 4.5% (95% CI: 2.7%-7.1%). These included four orofacial clefts, two atrial septal defects, one ventricular septal defect, one unspecified cardiac defect, one omphalocele, one hypospadias, one syndactyly, and two cases of Down syndrome, though the latter is unlikely to be associated with drug exposure. The Register currently reports 4 cases of orofacial clefts in 403 first trimester monotherapy exposures with *Lamictal Tablets* against an expected number of 1.0 based on data from the Swedish general population. The rate in lamotrigine monotherapy exposed pregnancies is 9.9 per 1000 versus a background general population rate of 2.0 per 1000 (data from 1995-2005).

European surveillance of congenital anomalies (EUROCAT) network

The EUROCAT central database contains standardized records of congenital malformations from 40 malformation registers in 20 countries across Europe. EUROCAT has captured congenital malformation information on live births and still births, from 20 weeks of gestation, and terminations of pregnancy following prenatal diagnosis since 1980.[104]

A population-based case control study evaluated first trimester exposure to lamotrigine monotherapy and risk of orofacial clefts relative to other major malformations.[104] Infants with major congenital malformations registered across 19 population-based malformation registers forming part of the EUROCAT network were included in the analysis. In the study, 85,563 non-chromosomal malformations met inclusion criteria including 5,511 non-syndromic clefts and 80,052 non-cleft malformed controls.

There were 72 malformed cases or controls exposed to *Lamictal Tablets*, 40 of these to lamotrigine monotherapy giving an exposure rate of 0.47/1000. There was no evidence of an increased risk of orofacial clefts (all non-syndromic or isolated or cleft palate) relative to other malformations with lamotrigine monotherapy versus no AED exposure. Adjusted odds ratios (95% confidence intervals) for maternal age: Isolated orofacial clefts, 0.80 (0.11 – 2.85); Non-syndromic clefts, 0.67 (0.10 – 2.34); Isolated cleft palate, 1.01 (0.03 – 5.57); Non-syndromic cleft palate, 0.79 (0.03 – 4.35).

Open-Label Studies

As part of an ongoing prospective study, Meador et al are examining the differential effects of *in utero* exposure to AEDs on the infant's subsequent neurodevelopment.[105] The includes pregnant women with epilepsy from 25 centers in the US and UK. The study will follow these children to determine if there are differential effects of the four most commonly used AEDs on cognitive and behavioral neurodevelopment at 6 years old. Interim data was published on 333 mother/child pairs receiving AEDs as monotherapy: CBZ (n = 110), *Lamictal Tablets* (n = 98), PHT (n = 56), and VPA (n = 69). For *Lamictal Tablets*, the rate of serious adverse outcomes (i.e., fetal death or congenital malformations) was 1%. The seizure-free rate during pregnancy was 80%. The mean dose was 393 mg/d in the first trimester. A second interim analysis reported IQ results at 2 years of age for 185 children (*Lamictal Tablets* n = 66, CBZ n = 48, PHT n = 42, VPA n = 29). [106] For *Lamictal Tablets*, the mean Mental Development Index (MDI) score adjusted for maternal IQ and anticonvulsant blood level was 94 and 11% of children had MDI scores < 70.

Dominguez-Salgado et al reported open-label results in 67 pregnant women (mean age, 28.9 years) with secondary generalized partial seizures treated with *Lamictal Tablets* as monotherapy over 4 years.[107] Among 67 patients, seven reported a seizure during pregnancy (n= 2 first trimester, n = 4 second trimester, n = 1 during delivery). Mean gestational age was 39 weeks. Fifty-three women had normal deliveries and nine had caesarean sections. No malformations were reported in children of mothers who received *Lamictal Tablets* as monotherapy throughout gestation (n = 62). A one-year follow-up study, completed in 57 of these newborns, revealed proper development without any evidence of malformation at 1, 3, 6, and 12 months of age.[108] Average APGAR was 8 at one minute and 9 at five minutes after birth. All anthropometric parameters, neurological examinations and developmental milestones were appropriate during follow-up.

Friedland et al prospectively evaluated women receiving AEDs during pregnancy and until one year postpartum.[109] Preliminary data was reported on 80 mother-child pairs with complete newborn records: *Lamictal Tablets* (n = 43), CBZ (n = 11), VPA (n = 8), levetiracetam (LEV, n = 6), PHT (n = 4), oxcarbazepine (OXC, n = 4), gabapentin (GBP, n = 3), topiramate (TPM, n = 3). All received monotherapy except two women receiving *Lamictal Tablets* and LEV. For each AED group, mean estimated gestational ages were > 37 weeks and mean APGAR scores were ≥ 7 except VPA (5.7) at one minute. The birth defect rate was 7.5% for all AEDs. One birth defect occurred with *Lamictal Tablets* and LEV. For *Lamictal Tablets* compared with all AEDs, rates of preterm births were 2.3% and 7.5%, respectively; low birth weight rates were 2.3% and 8.8%, respectively; small for gestational age rates were 9% and 20%, respectively; and neonatal intensive care unit admissions were 16.3% and 17.5%, respectively.

Chambers et al enrolled 62 pregnant women in an open-label study of newer AEDs that included a blinded dysmorphological exam for live born infants through the California Teratogen Information Service.[110] Treatments included GBP (n = 30), *Lamictal Tablets* (n = 19), TPM (n = 12), and GBP and *Lamictal Tablets* in combination (n = 1), for women with seizures, bipolar disorder, depression, pain, chronic fatigue syndrome, or fibromyalgia. Through January 2005, 47 women delivered live born infants of which 27 were examined for malformations. One infant who was exposed to *Lamictal Tablets* as monotherapy for seizures had coarctation of the aorta with anomalous left coronary artery, frontal hair upsweep, and a long philtrum. None of the nine examined infants exposed to *Lamictal Tablets* had >1 feature consistent with the anticonvulsant embryopathy.

Beach et al evaluated the extent of fetal and neonatal exposure with lithium and lamotrigine by studying maternal sera and umbilical cord blood pairs collected from 16 women at time of delivery at a single center.[111] Free lamotrigine was detectable in all maternal and umbilical cord samples with a placental passage of 1.20±0.29 (n = 6; mean dose, 525 mg/d and range, 150-1000 mg/d).

Myllynen et al studied transplacental passage of lamotrigine using an *ex vivo* human placental perfusion method and *in vivo* samples. [112] The umbilical cord blood/maternal lamotrigine concentration ratio (1.02 and 1.55) was also determined in the three epileptic mothers receiving *Lamictal Tablets* after delivery. Lamotrigine was detectable in the fetal circulation at 15 minutes and maternal fetal concentrations reached equilibrium at 60 minutes regardless of concentration.

LAMOTRIGINE PHARMACOKINETICS DURING PREGNANCY

There have been reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustment may be necessary to maintain clinical response. Adverse events due to lamotrigine toxicity were reported to occur from 3 days to 2 weeks following delivery.[113,114]

Pennell et al prospectively evaluated alterations in total and free lamotrigine clearance in 53 pregnant women (n = 39 epilepsy, n = 14 psychiatric diagnosis) to assess the impact of therapeutic drug monitoring on seizure frequency, to determine concentrations that are associated with increased seizure risk, and to evaluate maternal postpartum toxicity.[115] Analysis of 305 samples from 53 pregnancies demonstrated increased total and free lamotrigine clearance in all trimesters above baseline values in the preconception period ($P < 0.001$), with a peak increase of 94% and 89% in the third trimester. Free lamotrigine clearance was higher in white patients compared to African-American patients ($P = 0.031$). In the 36 women with epilepsy, increased seizure frequency in the second trimester was associated with a significantly lower ratio to target concentration (RTC) ($P < 0.001$). RTC < 0.65 was a reliable predictor of seizure worsening. An empiric postpartum taper (decreased dose at steady increments on postpartum days 3, 7, and 10 with return to preconception dose or preconception dose plus 50 mg) reduced the likelihood of maternal lamotrigine toxicity ($P < 0.05$). Newborn outcomes were similar to the general population.

Öhman et al prospectively evaluated pharmacokinetic alterations of lamotrigine and a major metabolite during 17 pregnancies in 15 women with epilepsy receiving *Lamictal Tablets*.[116] In the group with complete trough blood samples from all trimesters and baseline > 1 month after delivery (n = 12), the mean dose/plasma concentration ration (D/C) of lamotrigine at baseline was 66.5 ± 17.9 L/day and approximately 250% higher in late pregnancy. The mean lamotrigine-2-N-glucuronide/lamotrigine plasma concentration ratio (2-N-GLUC/LTG) was 0.349 ± 0.141 at baseline and 147% higher in late pregnancy. When including the 5 pregnancies with samples from the third trimester and baseline only, the 2-N-GLUC/LTG ratio was 175% higher in the third trimester compared to baseline ($P < 0.001$). Baseline values did not differ significantly between the pregnant women compared to a reference group of 20 non-pregnant women (aged 17-45 years) receiving *Lamictal Tablets*.

Pennell et al examined the alterations in free lamotrigine clearance in 12 pregnant women (n = 11 epilepsy, n = 1 bipolar disorder) to determine the transplacental passage of lamotrigine during pregnancy.[117] Apparent clearance (AC, calculated as daily dose [mg]/concentration [mg/L]) and relative clearance (RC, calculated as daily dose [mg/kg]/concentration [mg/L]) are shown in Table 11. A statistically significant main effect of perinatal stage on free lamotrigine clearance was observed ($P < 0.01$). Clearance increased during the first trimester compared to postpartum values and peaked at approximately 185% of baseline postpartum values. No major malformations were reported.

Table 11. Free Lamotrigine Apparent and Relative Clearance Across Perinatal Intervals in Pennell et al study [117]

	1st trimester [mean (SD)]	2nd trimester [mean (SD)]	3rd trimester [mean (SD)]	Postpartum [mean (SD)]
Apparent clearance (AC) of Lamotrigine				
Samples (n)	15	26	40	26
AC, mg/(mg/L)	210.5 (159.2)	271.7 (151)	287.6 (144.4)	159.7 (103.4)
Relative clearance (RC) of Lamotrigine				
Samples (n)	12	25	24	21
RC (mg/kg)/(mg/L)	3.04 (2.56)	4.17 (2.42)	3.47 (1.72)	2.19 (1.07)
AC = apparent clearance, RC = relative clearance, SD = standard deviation				

Pennell et al retrospectively evaluated changes in lamotrigine clearance during pregnancy in 14 women with epilepsy receiving *Lamictal Tablets* as monotherapy. [113] The primary outcome measures were AC

and RC (weight-adjusted). AC was calculated for each of the 128 concentration samples (from 14 patients) and reported as percentage change from that individual patient's baseline AC. Mean percentage changes from baseline for AC and RC (secondary outcomes) are reported in Table 12. Lamotrigine AC values progressively increased throughout pregnancy and reached a peak of >330% of baseline clearance by week 32. Lamotrigine clearance began to decline after 32 weeks and rapidly returned to preconception baseline values in the postpartum period. In the first 2 weeks postpartum, several participants reported toxicity before sufficient dose adjustments occurred. RC was calculated using 88 samples (from 12 patients) and demonstrated a similar trend. The data also revealed considerable interindividual variability.

Table 12. Lamotrigine Apparent Clearance and Relative Clearance Across Perinatal Intervals [113]

Parameter	Pre-conception [mean (SD)]	First trimester [mean (SD)]	Second trimester [mean (SD)]	Third trimester [mean (SD)]	Postpar-tum [mean (SD)]	Perinatal interval by ANOVA
Apparent clearance (AC) of Lamotrigine						
Samples (n)	9	18	27	35	20	-
AC, mg/(mg/L)	52.9 (20.8)	88.5 (40.9)	132.5 (70.7)	171.2 (100.3)	65.6 (29.2)	$P < 0.0001$
% change AC	-	191.1 (106.7)	284.8 (141.5)	361.2 (194.3)	149.6 (69.0)	$P < 0.0001$
Relative clearance (RC) of Lamotrigine						
Samples (n)	5	10	16	18	3	-
RC, (mg/kg)/(mg/L)	0.71 (0.24)	1.55 (1.02)	1.93 (1.22)	2.19 (1.09)	0.74 (0.11)	$P < 0.0008$
% change RC	-	231.0 (128.1)	280.6 (139.3)	332.6 (149.1)	137.5 (58.4)	$P < 0.0524$
AC = apparent clearance, ANOVA = analysis of variance, RC = relative clearance, SD = standard deviation						

Tomson et al retrospectively evaluated changes in the dose of *Lamictal Tablets* during pregnancy in women receiving *Lamictal Tablets* 100-500 mg/d as monotherapy or with clonazepam or topiramate (n = 8) or in combination with valproate (VPA) 500-2000 mg/d (n = 6).[118] The mean dose/plasma concentration ratio (±SD) of *Lamictal Tablets* increased 295% from baseline (57.9 ± 18.7 L/d) in women receiving monotherapy and 60% from baseline (13.9 ± 6.8 L/d) in women receiving adjunctive VPA. In the monotherapy group, the change from baseline was significant in early pregnancy ($P < 0.05$) and midpregnancy ($P < 0.001$). In the four women with available dose/plasma concentrations from late pregnancy in the monotherapy group, the values were similar to those in midpregnancy. The dose/plasma concentration ratio of *Lamictal Tablets* was significantly higher among women treated with monotherapy compared to women receiving adjunctive VPA at baseline and during all periods of pregnancy. The dose of *Lamictal Tablets* remained unchanged in all 6 women receiving VPA and was increased in 6 of the women receiving monotherapy.

Tran et al conducted a retrospective, observational study of lamotrigine clearance during pregnancy in 11 women with epilepsy (n = 12 pregnancies). [119] AC was calculated whenever dose, serum level of lamotrigine, and patient's weights were available and compared between preconception and each trimester. Two patients received *Lamictal Tablets* as monotherapy and the remaining 9 received concomitant AEDs. Lamotrigine dose and levels were only used if dose was stable for 2 weeks at time of sampling. A >65% increase in AC between preconception and the first 2 trimesters ($P < 0.05$) was observed. No significant change in AC was noted between each trimester or between preconception and postpartum. There was a decrease in AC between the last 2 trimesters and postpartum ($P < 0.05$) which occurred as early as 2 weeks postpartum. An inverse relationship existed between AC and serum levels; thus with a sharp drop in AC, postpartum lamotrigine levels increased 2-3 fold. AC returned to preconception baseline shortly after delivery requiring a dose reduction of *Lamictal Tablets*. Wide interpatient variability in changes in AC were also reported.

Petrenaite et al retrospectively evaluated seizure deterioration and changes in the ratio of lamotrigine plasma level:dose in 11 pregnant women (22-30 years) with epilepsy receiving *Lamictal Tablets* as monotherapy. [120] The mean daily dose of *Lamictal Tablets* before pregnancy was 286 mg/d (range 75-750 mg/d) and during the third trimester, was 570 mg/d (range 200-1100 mg/d). A significant decrease in the

ratio of plasma lamotrigine concentration:dose by 65.1% was observed during the second trimester (P = 0.0058) and by 65.8% during the third trimester (P = 0.0045) compared to pre-pregnancy values. After delivery, the ratio returned to pre-pregnancy values. Wide interpatient variability in changes in ratio were also reported. Five patients experienced seizure deterioration during pregnancy, which mostly occurred between the 18th and 35th gestational week. All patients that had a ratio reduction of >60% experienced seizures in the second trimester.

de Haan et al conducted a retrospective observational study to explore gestation-induced pharmacokinetic changes in 9 women (12 pregnancies) with epilepsy receiving *Lamictal Tablets* as monotherapy. [114] Seizure aggravation was observed in 9 of 12 pregnancies (seizure recurrence n = 3, recurrence of tonic-clonic seizures n = 1, new-onset tonic-clonic seizures n = 1, and increased seizure frequency n = 4) and occurred between weeks 12 and 28 in 8 pregnancies and week 40 in one pregnancy. Doses of *Lamictal Tablets* were increased to regain seizure control in 7 women. Three of these 7 women (lamotrigine levels of 12-14 mg/L) reported dizziness, diplopia and ataxia occurring 3-10 days after delivery. Mean level-to-dose ratios for successive 10-week gestation periods were: 82%, 51%, 40%, and 48% of baseline, and 97% post-delivery.

Öhman et al measured plasma concentrations of lamotrigine in 9 women (10 pregnancies) with epilepsy at time of delivery and 2 weeks later.[121] Baseline blood samples were drawn ≥2 months before (n = 1) or after pregnancy (n = 8). Daily doses of *Lamictal Tablets* ranged from 100-800 mg/d. Five patients received *Lamictal Tablets* as monotherapy, including one woman with a current and previous pregnancy; while four received *Lamictal Tablets* as adjunctive therapy with carbamazepine (n = 2), phenytoin (n = 1), or valproate (n = 1). There was a significant increase in the plasma concentration/dose ratios from delivery to the sampling periods 2-3 weeks after delivery (P < 0.05). The median increase was 170% (range, 0-630%). The ratios at delivery were significantly lower compared with baseline values ≥2 months before or after pregnancy (P < 0.05); although in one patient receiving phenytoin and another receiving carbamazepine, there was no increase in this ratio after delivery.

Use During Lactation

Newport et al studied lamotrigine excretion into breast milk and safety to nursing infants in a prospective, observational study of 30 women with epilepsy (63%) or bipolar disorder (37%) who elected to continue *Lamictal Tablets* during lactation.[122] Breast milk samples (10 mL) were collected for time course (foremilk collected every 4 hours over 24 hours) or gradient (aliquots from fore milk to hind milk) analyses. Each sample was analyzed as milk/plasma (M/P) ratios of the minimum, maximum, and mean breast milk concentration. Theoretical and relative infant doses (TID and RID, respectively) were calculated to estimate infant drug exposure, and infants were monitored for adverse effects for up to one year.

A total of 210 breast milk samples were collected at a mean of 13 weeks postpartum. Lamotrigine concentrations in breast milk ranged from 0.5 to 11.77 mcg/mL (mean, 3.38 mcg/mL). The lamotrigine concentration in breast milk 4 hours post dose was high, but this was not significant. Gradient analysis from 94 samples revealed lower concentrations of lamotrigine in hind milk. Maternal daily dose of *Lamictal Tablets*, total lamotrigine concentration in maternal plasma, and the free lamotrigine concentration in maternal plasma significantly correlated with breast milk concentration (P < 0.001, all). Mean breast milk to maternal serum ratio (n = 26) was 0.41 (range, 0.13-1.05). The TID and RID were 0.51 mg/kg/day and 9.2%, respectively. No infants exhibited malformations, or rash; and among infants with blood draws, none had significant abnormalities electrolyte counts (n = 10), liver function tests (n = 10), or hematocrit values (n = 8). Seven of the 8 infants exhibited elevated platelet counts (mean 520.5, range 329.0 - 652.0), but no adverse clinical outcomes were observed in this group. Mean total lamotrigine concentration in the infants was 1.2 mcg/mL (range, <0.3-3.9 mcg/mL).

Öhman et al also measured plasma and milk concentrations of lamotrigine using reversed-phase high-performance liquid chromatographic (HPLC) in 9 pregnant women with epilepsy (WWE) and lamotrigine plasma levels in their 10 infants.[121] After two weeks, blood and milk samples was drawn from the mother and infant before and after breast-feeding and 11-15 hours after the mother took her last dose of *Lamictal Tablets*. Baseline blood samples were drawn from the mothers ≥2 before (n = 1) or after pregnancy (n = 8). Daily doses of *Lamictal Tablets* ranged from 100-800 mg/d. Six patients received *Lamictal Tablets* as monotherapy (n = 5), 1 woman had her current plus a previous pregnancy reported; while 2 were also receiving carbamazepine, 1 receiving phenytoin, and 1 receiving valproate.

The median milk/maternal plasma lamotrigine ratio was 0.61 (range, 0.50-0.77) before nursing with minor changes thereafter. The minimal daily estimated lamotrigine intake by the infant during breast-feeding was 0.2-1 mg/kg/d, assuming a daily milk intake of 150 mL/kg/d. The authors calculated that this corresponded to 9% (median, range 2-20%) of the weight-adjusted maternal daily dose. Median plasma concentrations of lamotrigine in the breast-fed infants were approximately 30% (range, 23-50%) of the maternal lamotrigine concentrations.

Page-Sharp et al studied the transfer of lamotrigine into breast milk in six women (ages, 30-38 years) receiving *Lamictal Tablets* 175-800 mg/d (mean, 400 mg/d) for epilepsy (n = 5) or bipolar disorder (n = 1).[123] Five of the 6 infants breast-fed exclusively and one breast-fed 50%. The median infant age was 4.1 months (0.4-5.1, all >12 days) and median infant weight was 5.6 kg (3-8) on the study day. Milk samples were collected by hand expression at various times (up to 14 times per patient) over 1 or 2 dose intervals. Mean absolute infant doses of lamotrigine were 0.45 mg/kg/day (95% Confidence Interval [CI], 0.25-0.65), mean relative infant doses were 7.6% (95% CI, 6.2-9.1), and mean infant/maternal plasma values were 18% (95% CI, 6-30). No adverse effects were reported in the mothers or in the 3 assessed infants.

Folvary-Schaefer et al measured breast milk penetration of lamotrigine in a prospective study of pregnant women with epilepsy receiving *Lamictal Tablets*.[124] In mothers electing to breastfeed, maternal plasma and breast milk concentrations and infant plasma concentrations of lamotrigine were determined at 1 week and at 3 months postpartum. Eleven mother-infant pairs participated in the study and 5 infants were breastfed. Fifty-two maternal, 39 neonatal and 7 breast milk samples were obtained. All breast-feeding mothers received *Lamictal Tablets* as monotherapy. The following preliminary results were calculated: mean breast milk penetration (milk/maternal concentration) = 0.526 ± 0.212, mean breast feeding ratio (nursing neonate concentration/maternal concentration) = 0.550 ± 0.387, and median relative infant dose (dose infant/dose maternal x 100) for breastfed infants = 2.073 (0.641 - 2.439) compared with 0.544 (0.421 - 1.579) for non-breastfed infants. No adverse effects were observed in the infants during 3 months of evaluation.

Liporace et al obtained serum lamotrigine levels in 4 lactating mothers (and their infants) receiving *Lamictal Tablets* as monotherapy. [125] Serum lamotrigine levels in the 4 infants were <1, 1.3, 1.8 and 2 mcg/mL on day 10 of life. After excluding one child with an undetectable level, lamotrigine levels in the infants were on average 30% (range, 20-43%) of maternal levels. No decline was noted in 2 infants with repeat levels at 2 months.

de Haan et al conducted a retrospective observational study of 9 WWE (n = 12 pregnancies) receiving *Lamictal Tablets* as monotherapy. [114] The mean milk/maternal plasma concentration was 0.54 in 3 samples. One breast-fed infant had a lamotrigine serum concentration 1.7 mg/L at 10 days after delivery which was 30.4% of the mother's plasma level.

4.6 Pharmacology

clinical Information

Lamictal, an antiepileptic drug (AED) of the phenyltriazine class, is chemically unrelated to existing AEDs.[1] Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine and its molecular formula is $C_9H_7N_5Cl_2$. The precise mechanism(s) by which lamotrigine exerts its action in epilepsy and bipolar disorder are unknown.

Models of anticonvulsant activity

The anticonvulsant activity of lamotrigine has been studied in several animal models of epilepsy and compared with currently available AEDs. [126] [127] [128] [129,130] The relevance of these models to human epilepsy, however, is not known. In mice and rats, lamotrigine was effective in preventing seizure spread in the maximum electroshock (MES) and pentylenetetrazol (PTZ) tests and prevented seizures in the visually and electrically evoked after discharge tests for antiepileptic activity, suggesting activity in primary and secondarily generalized seizures as well as partial seizures.[1] [126] Lamotrigine was also effective in several other models of chemically-induced seizures, including bicuculline, picrotoxin, and strychnine. Lamotrigine was active in the electrically evoked after-discharge model in several species, which suggests activity against simple and complex partial seizures. [127] Lamotrigine also reduced cortical kindling in rats, which is regarded as a model for complex partial seizures. [128] [131] Lamotrigine was ineffective in

preventing PTZ-induced facial and forelimb clonus (a model of absence seizures) [126], but was active in another model, the visually evoked after-discharge test.[130] *Lamictal* also displayed inhibitory properties in the kindling model in rats both during kindling development and in the fully kindled state.[1] The relevance of this animal model to specific types of human epilepsy is unclear.

Ion channel effects

Sodium

In vitro pharmacological studies suggest that lamotrigine inhibits voltage sensitive sodium channels, thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).[1] [132] [133] [134] [135] Several authors have theorized that the relatively broader spectrum of activity of lamotrigine may be due to markedly preferential affinities to certain sodium-channel subunit combinations, exhibiting differential regional distributions in the brain. [136] Xie et al studied the effect of lamotrigine on rat brain type IIA sodium channels expressed in cell lines and found tonic inhibition of sodium currents occurs in a concentration-dependent and voltage-dependent manner. [137] Their results suggested that lamotrigine's effects might primarily be due to stabilization of the slow inactivated state of the channel. Lamotrigine may shift the voltage dependence of inactivation to more hyperpolarized potentials and slow the time course of recovery from activation.

Kuo examined the inhibition of sodium currents by studying a mixture of lamotrigine, phenytoin (PHY), and carbamazepine (CBZ). [138] Their findings suggested that all of these agents bind to a common receptor located on the extracellular side of the sodium channel. Because of much higher affinities to the inactivated state than to the resting state of the sodium channel, the anticonvulsant receptor may not exist in the resting state and may undergo conformational changes to make the receptor on the extracellular side of the sodium channel. In dissociated rat hippocampal granule neurons in a pilocarpine model of chronic epilepsy, lamotrigine (100 μM) had modest tonic blocking effects on sodium channels in their resting state, shifted the voltage dependence of activation in a depolarizing direction, and potently slowed the time course of fast recovery from inactivation. [139] Cronin et al found that lamotrigine preferentially bound sodium channels in the inactivated open state and produced a conformational change in the voltage-dependent sodium channel structure. [140]

Calcium

Initial studies failed to detect an effect of lamotrigine on dihydropyridine sensitive calcium channels.[1] However, scientific evidence has demonstrated potential blockade of high-voltage-activated calcium channels by lamotrigine. [141] [142] [143] [144] Lamotrigine was observed to cause a large reduction in high-voltage-activated calcium currents and a smaller, use-dependent inhibition of sodium conductance of isolated neurons from the adult rat neocortex. [142] In a low magnesium-induced model of epilepsy, lamotrigine reduced the frequency of occurrence of low-magnesium induced field potentials in CA1 and CA3 areas of the hippocampus slice preparation (guinea pigs) in a dose-dependent manner. [145] The results indicated that lamotrigine behaves in an additive manner with verapamil and CBZ and may share common actions on the same calcium channel subtype. Stefani et al found that lamotrigine consistently inhibited voltage-activated calcium currents in rat cortical and striatal neurons at clinically relevant concentrations and lamotrigine also reduced calcium conductances involved in the regulation of neurotransmitter release. [146] Using whole-cell patch-clamp recordings from isolated neocortical neurons, Pisani et al demonstrated with both lamotrigine and levetiracetam were able to reduce the amplitude and duration of paroxysmal depolarization shifts, as well as the concomitant elevation in calcium, in a dose-dependent fashion. [147] Wang et al also reported that lamotrigine reduced depolarization-evoked calcium influx in a concentration-dependent manner. [148] [149] [144] This inhibitory effect was associated with a reduction in the depolarization-evoked increase in the cytoplasmic free calcium concentration. These calcium channel effects appeared to be mediated, at least in part, by the modulation of N-type calcium channels. The authors suggested that presynaptic calcium influx blockade and inhibition of glutamate release may underlie therapeutic mechanisms of lamotrigine. In another study, lamotrigine (10 μM) inhibited R-type calcium channel currents (30%) and had little to no effect on T-type currents. [150] Additionally, lamotrigine's effects on neuronal P-type calcium channels have been described. [151]

Potassium

Results have suggested that lamotrigine modulates the transient potassium outward current I_D from *in vitro* models using whole cell patch clamp recordings from rat CA1 pyramidal cells. (152) Zona et al used field-potential recordings in slices of rat cerebral cortex along with whole-cell patch recordings from rat neocortical cells in culture to test lamotrigine's effect on potassium-mediated, hyperpolarizing currents. (153) Lamotrigine (100-400 μM) reduced and/or abolished epileptiform discharges induced by 4-aminopyridine (4AP, 100 μM; n = 10), at doses that were significantly higher than those required to affect epileptiform activity recorded in magnesium-free medium (n = 8). Additionally, lamotrigine (100-500 μM; n = 13) increased a transient, 4AP-sensitive, outward current elicited by depolarizing commands in medium containing voltage-gated calcium and sodium channel antagonists. Increasing the fast transient potassium current may control aberrant excitation and therefore contribute to lamotrigine's activity. (153)

Lamotrigine (30 μM-3 mM) also caused a reversible reduction in the amplitude of A-type potassium current in embryonal hippocampal neurons. (154) The median inhibitory concentration (IC_{50}) value required for the inhibition was 160 M. In addition, lamotrigine (100 M) produced a significant prolongation in the recovery of potassium current.

N-methyl-D-aspartate (NMDA)

Lamotrigine did not inhibit N-methyl-D-aspartate (NMDA)-induced depolarizations in rat cortical slices or NMDA induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine displace compounds that are either competitive or noncompetitive ligands at this glutamate receptor complex (CNQX, CGS, TCHP).(1) The IC_{50} for lamotrigine effects on NMDA induced currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded 100 μM.

In rats, lamotrigine 20-160 mg/kg did not produce phencyclidine-like effects, suggesting that lamotrigine does not act by direct inhibition of the NMDA receptor.(155) Brown et al tested whether lamotrigine and other agents have protective properties against the ultrastructural changes induced by NMDA, AMPA or thapsigargin.(156) Their preliminary results demonstrated that lamotrigine (0.1 mM) only protected against the damage caused by thapsigargin exposure. However, in NMDA antagonist models, lamotrigine 20-30 mg/kg intraperitoneally (IP) prevented the disruption of prepulse inhibition and reduced the deficit in reversal learning induced by ketamine, but not *d*-amphetamine in mice.(157,158)

Neurotransmitter effects

In vitro studies comparing the effectiveness of lamotrigine in inhibiting veratrine-induced release of various neurotransmitters showed that lamotrigine is a more potent inhibitor of glutamate and aspartate release than GABA release. (132) *In vivo* studies in rats found that lamotrigine 20 mg/kg significantly reduced basal levels of glutamate and aspartate, but did not affect taurine or GABA. (159) (160) Lamotrigine 10 mg/kg inhibited veratridine-induced release of all 4 neurotransmitters, although most marked for glutamate.

Glutamate and Gamma-aminobutyric acid (GABA) effects

Several studies in ischemic models in animals have demonstrated that lamotrigine attenuates the surge of glutamate following the ischemic insult. (161,162) (163) (164) Other *in vitro* studies have also reported a potential presynaptic site for glutamatergic action. (135,165) Lingamaneni and Hemmings compared the effects of 3 conventional (phenytoin [PHY], carbamazepine [CBZ] and phenobarbital [PB]) and 3 novel (lamotrigine, riluzole, and BW 1003C87) AEDs on evoked glutamate release from rat cortical synaptosomes. (135) Their results found that therapeutic concentrations of lamotrigine inhibited veratridine-evoked glutamate release and inhibited synaptic glutamate release by preferentially blocking presynaptic sodium channels. In an electrophysiological study, lamotrigine (10-300 μM) was reported to decrease neuronal excitability by modulating multiple sites of action in rat corticostrial tissue.(165) Neither resting membrane potential nor the input resistance/membrane conductance was affected. However, the current-evoked repetitive firing discharge was depressed in a dose dependent and reversible manner and the amplitude of glutamatergic excitatory postsynaptic potentials (EPSPs) evoked by cortical stimulation were reduced. Lamotrigine preferentially inhibited corticostriatal excitatory transmission. Lamotrigine also depressed cortically-evoked EPSPs increasing paired-pulse facilitation (PPP) of synaptic transmission; this suggested a presynaptic site of action.

Lamotrigine has been reported to affect GABA-mediated synaptic transmission, but there are conflicting reports as to whether it enhances or suppresses inhibitory transmission. In receptor binding assays, lamotrigine did not exhibit high affinity binding (IC_{50}>100 μM) to $GABA_A$ and $GABA_B$.(1)

Cunningham and Jones examined the effect of lamotrigine on the release of glutamate and GABA at synapses in the rat entorhinal cortex using the whole-cell patch clamp technique to record spontaneous excitatory (EPSCs) and inhibitory postsynaptic currents (IPSCs). (166) Lamotrigine reduced the frequency, but not the amplitude of spontaneous EPSCs, which indicated a presynaptic effect to reduce the release of glutamate. In contrast, lamotrigine increased both the frequency and amplitude of spontaneous IPSCs, suggesting a presynaptic action to enhance GABA release. The investigators reported that these opposite effects on glutamate and GABA release are similar to those previously reported with PHY, and suggest that reciprocal modulation of the background release of the major excitatory and inhibitory transmitters may be a significant factor in dampening excitability in pathologically hyperexcitable cortical networks. However, a conflicting study found lamotrigine to have no influence on the induction and maintenance of long-term potentiation and no presynaptic activity. (167)

Braga et al examined the effects of lamotrigine on $GABA_A$ receptor-mediated synaptic transmission in slices from rat amygdala.(168) In intracellular recordings, lamotrigine (100 μM) reduced $GABA_A$ receptor-mediated IPSPs evoked by electrical stimulation in neurons of the basolateral nucleus. In whole-cell recordings, lamotrigine (10, 50 and 100 μM) decreased the frequency and amplitude of spontaneous IPSCs, as well as the amplitude of evoked IPSCs, but had no effect on the kinetics of these currents. Lamotrigine also had no effects on the frequency, amplitude or kinetics of miniature IPSCs recorded in the presence of tetrodotoxin, a sodium channel blocker. Their results suggested that lamotrigine suppresses $GABA_A$ receptor-mediated synaptic transmission by a direct and/or indirect effect on presynaptic calcium influx in the basolateral amygdala. They postulated that modulation of inhibitory synaptic transmission may be an important mechanism underlying the psychotropic effects of lamotrigine. In a gene expression study, another investigator found that chronic treatment with lamotrigine upregulated the gene expression for $GABA_A$ receptor beta 3 subunit in CA1, CA3 and dentate gyrus of rat hippocampus. (169)

Shiah et al examined the effects of lamotrigine (100 mg/day for 1 week) on plasma GABA levels in healthy volunteers (n = 11).(170) No significant difference in plasma GABA levels before and after treatment with lamotrigine were detected. These findings suggested that lamotrigine 100 mg/day does not appear to enhance GABA levels in humans. The investigators of an additional study found no significant effects of lamotrigine on platelet uptake of GABA in 14 patients with juvenile myoclonic epilepsy. (171) However, in a randomized study of healthy volunteers, cerebral GABA concentrations significantly increased (25%) versus baseline after 4 weeks of lamotrigine, but not during acute treatment. (172)

Monoamines

Following lamotrigine (30 mg/kg) administration to rats, there was no or minimal reduction in monoamine (MAO) A and B activities when assayed *ex vivo*.(173) *In vivo* brain microdialysis did not detect meaningful alterations in extracellular hippocampal or frontal cortex MAO concentrations. Therefore, lamotrigine is unlikely to have clinically significant effects on MAO.

In receptor binding assays, lamotrigine had a weak inhibitory effect on the serotonin (5-HT) type 3 receptor (IC_{50}=18 μM) and did not exhibit high affinity binding (IC_{50}>100 μM) to dopamine (D_1 and D_2) and $5\text{-}HT_2$.(1) Lamotrigine did not inhibit the uptake of norepinephrine, dopamine, or serotonin (IC_{50}>200 μM) when tested in rat synaptosomes and/or human platelets *in vitro*.

In vitro and *in vivo* studies have yielded potential evidence of $5\text{-}HT_{1A}$ receptor blocking effects by lamotrigine. (174) (175,176) In rats, oral administration of lamotrigine (5 mg/kg) for 7 days significantly decreased the density of cortical (50%, $P < 0.001$) but not hippocampal $5\text{-}HT_{1A}$ receptors, indicating potential changes in serotonergic transmission. (175) However, a study 10 healthy male volunteers receiving *Lamictal* 100 mg/day x 1 week found no significant alteration in hypothermic or cortisol responses to ipsapirone.(177) A study of $5\text{-}HT_{1A}$ receptor binding by positron emission tomography included 10 patients with epilepsy receiving *Lamictal* (mean dose, 385 mg/day) and reported that the mechanism of action for lamotrigine is unlikely to be strongly related to $5\text{-}HT_{1A}$ receptors.(178)

Studies of the forced swimming test in mice investigated the effect of *Lamictal* on the noradrenergic system.[179,180] Kaster et al reported that lamotrigine (20-30 mg/kg, intraperitoneally [IP]) decreased immobility time and number of crossings in the open-field test.[179] In addition, pretreatment with alpha-methyl-p-tyrosine (100 or 250 mg/kg IP; an inhibitor of tyrosine hydroxylase), prazosin (1 mg/kg IP, an $alpha_1$-adrenoceptor antagonist), or yohimbine (1 mg/kg IP, an $alpha_2$-adrenoceptor antagonist) prevented the anti-immobility effect of lamotrigine. Administration of subeffective doses of phenylephrine (5 mg/kg IP, an $alpha_1$-adrenoceptor agonist) or clonidine (0.06 mg/kg IP, an $alpha_2$-adrenoceptor agonist) potentiated the action of a subeffective dose of lamotrigine (10 mg/kg IP). These results suggest that the antidepressant-like effect of lamotrigine in the forced swimming test is related to the noradrenergic system. A separate study of the modified forced swimming test reported noradrenergic effects with lamotrigine (20 mg/kg IP) that were not dependent on sodium sensitive channel blockade.[180]

Ahmad et al studied the effects of acute and chronic treatment with lamotrigine on basal and stimulated extracellular 5-HT, dopamine (DA) and their metabolites in the hippocampus of freely moving rats using *in vivo* microdialysis. [181] Acute lamotrigine (10 and 20 mg/kg) treatment decreased extracellular 5-HT, but had no effect on its metabolite 5-hydroxyindoleacetic acid (5-HIAA). Dialysate DA was also decreased by lamotrigine as were its metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). However, lamotrigine had no effect on veratridine-evoked transmitter release. In chronic experiments, after 2-7 days of treatment with lamotrigine, (5 mg/kg BID) 5-HT and DA concentrations were significantly increased in treated versus control rats but returned to basal values thereafter. Lamotrigine had no effect on extracellular DOPAC, but HVA followed a similar pattern to its parent transmitter. Lamotrigine also had no effect on stimulated DA release. In a similar model, Ahmad et al reported that lamotrigine (10-20 mg/kg) caused a dose-dependent decrease in basal extracellular 5-HT and DA and had no effect on veratridine-evoked release of extracellular 5-HT and DA. [160]

Other Neurotransmitters

Lamotrigine does not exhibit high affinity binding (IC_{50}>100 μM) to the following other neurotransmitter receptors: adenosine A_1 and A_2; adrenergic α1, α2, and β; histamine H_1; kappa opioid; and muscarinic acetylcholine.[1] It had weak effects at sigma opioid receptors (IC_{50}=145 μM).

Effects on other study models of neuronal excitability

Hyperpolarization-activated cation current (I_h, h-channel)

Poolos et al investigated the differential effects of lamotrigine on the excitabilty of dendrites and somata using whole-cell and cell-attached recordings in rat hippocampal slices. [182] Lamotrigine (50-100 μM) caused a modest reduction of repetitive action potential firing during current injection at the soma (83% of control, n = 6; $P < 0.0001$). However, when a similar rate of actional potential firing was elicited from a dendritic injection site, lamotrigine markedly reduced or abolished action potential firing (17% of control, n = 8). Lamotrigine abolished action potential firing for all but the highest amplitude current injections. In addition, lamotrigine caused a concentration-dependent depolarization of resting potential which was similar in the soma and dendrites. Lamotrigine did not affect the amplitude of back-propagating action potential or the decrement due to dendritic sodium current entering into a slow inactivated state. Therefore, the authors stated that this effect on dendrite excitability was not due to action on sodium channels, but rather to an increase in Ih, a voltage-gated current present in high-density dendrites. This mechanism of action may provide an explanation for lamotrigine's efficacy against generalized seizures and suppression of excessive firing while unaffecting normal brain function. Berger and Luscher also reported that lamotrigine (50-100 μM) caused an increase in Ih in layer V pyramidal cells of rat cortex, but dendritic input to the soma was not attenuated.[183] They commented that the effects of therapeutic concentrations of lamotrigine on Ih are likely of less significance than those on sodium channels.

Transcranial magnetic stimulation (TMS)

Studies using TMS have described motor threshold elevations in human volunteers and patients following treatment with *Lamictal*. [184] [185] [186] [187] [188,189] One randomized, double-blind, placebo-controlled, crossover study of 14 healthy volunteers used TMS and functional magnetic resonance imaging (MRI) to help assess the effects of lamotrigine (single oral dose of 325 mg) on activated motor or prefrontal/limbic circuits. [187] Through a complex effect on prefrontal TMS, lamotrigine, at clinically relevant serum concentrations, had an inhibitory effect on cortical neuronal excitability and an activating effect in

limbic regions (n = 10). In a randomized, placebo-controlled crossover study of 16 healthy volunteers, Tergau et al evaluated the relationship between lamotrigine oral dosages, serum levels and inhibitory effects on resting motor threshold (r-MT) using TMS. (186) Subjects received lamotrigine (325 mg) as a single dose, as bi-hourly graded cumulative dose, or placebo. With single dose, r-MT elevation showed a poor but significant correlation to serum levels. With graded dose, serum levels as well as r-MT increased dose-dependently with significant linear correlation ($P < 0.0001$). Lee et al also demonstrated a positive correlation between TMS measures of cortical excitability and plasma blood levels of lamotrigine following 5 weeks of administration (final dose of 100 mg BID) to 10 healthy volunteers. (188) r-MT increased with increasing lamotrigine levels ($P < 0.0001$) and rapidly normalized following acute discontinuation. A double-blind, placebo-controlled study of AEDs (including lamotrigine) in 10 healthy volunteers found that lamotrigine increased both r-MT and active motor threshold (a-MT), markers of axon excitability controlled by voltage-gated sodium channels.(189)

Nitric oxide

The effects of lamotrigine and CBZ on the release of preloaded D-[3H]aspartate and the involvement of nitric oxide were studied with mouse cerebral cortical slices in a superfusion system. (190) Lamotrigine inhibited the veratridine-evoked release, while potassium-stimulated release was attenuated more strongly by CBZ than lamotrigine. Another investigator reported that lamotrigine (20 mg/kg IP), when administered 30 minutes before or just after focal cerebral ischemia, produced a marked reduction in cortical and cerebellar levels of both nitrite and cGMP.(191) Other investigators reported that lamotrigine (20 mg/kg IP), when administered 60 minutes before penthylenetetrazole-induced epileptiform seizures in rats, significantly reduced enhancement of nitric oxide generation, prevented increases in thiobarbituric acid reactive substances formation, and decreased tonic seizures.(192)

4.7 Pharmacokinetics/Pharmacodynamics

Refer to Enclosed Prescribing Information.

4.8 Contraindications

Refer to Enclosed Prescribing Information.

4.9 Warnings/Precautions

Refer to Enclosed Prescribing Information.

4.10 Adverse Events

Refer to Enclosed Prescribing Information.

4.11 Other Clinical Considerations

Refer to Enclosed Prescribing Information.

4.12 Drug/Food/Disease Interactions

Refer to Enclosed Prescribing Information.

4.13 Dosing and Administration

Refer to Enclosed Prescribing Information.

4.14 Co-prescribed/Concomitant Therapies

Refer to Enclosed Prescribing Information.

CLinical Information

The effectiveness of monotherapy with *Lamictal* at doses of 100-400 mg/day(d) as maintenance treatment of bipolar I disorder was established in two multicenter, double blind, placebo controlled, 18-month studies. (11,12) (10) One enrolled adult patients with bipolar I disorder who presented with a current or recent manic or hypomanic episode (n = 349) and the other enrolled currently or recently depressed patients (n = 966). Lithium was used as an active control in these studies, but the design does not allow for comparison between *Lamictal* and lithium. During the 8-16-week open-label phase, *Lamictal* was titrated to a target dose of 100-200 mg/d as add-on therapy or as monotherapy, while concomitant psychotropic medications

were gradually withdrawn. Eligible patients were then randomized to treatment with *Lamictal*, lithium or PBO for up to 18 months. Across both studies, *Lamictal* and lithium (0.8-1.1 mEq/L) were associated with statistically significant differences versus PBO on delaying time to intervention for a mood episode and overall survival in study. Intervention was defined as the addition of pharmacotherapy (eg, antipsychotics, antidepressants) or ECT for a bipolar mood episode or one that was emerging.

In a post-hoc analysis of the combined studies, Bowden et al examined the tolerability and effectiveness among patients receiving concomitant lithium during the open-label, dose escalation phase (n = 292, 29%).[193] The mean co-exposure was eight weeks and mean doses were 102 mg/day for *Lamictal* and 902 mg/day for lithium. Improvement in mean rating scale scores and incidence of adverse events were similar between patients receiving this combination versus patients receiving *Lamictal* without lithium. No cases of serious rash were reported in patients taking *Lamictal* and lithium, and there was a similar incidence of rash between patients who received *Lamictal* and lithium versus those not receiving *Lamictal* with lithium (9% vs. 11%).

Another post-hoc analysis of clinical response and adverse-event profiles in patients (mean age, 42 years) treated with *Lamictal* with or without concomitant lithium was conducted from a prospective, open-label study in patients with bipolar I disorder designed to assess the rate of rash in patients with or without specific dermatological precautions.[194,195] *Lamictal* was administered alone or in combination with other medications for 12 weeks, including a 5-week titration period. Of the 1175 patients included in the study, 267 (23%) were receiving concomitant lithium.[194] Statistically significant improvement from baseline was observed with *Lamictal* with and without lithium based on mean Clinical Global Impression-Bipolar version (CGI-BP) Severity Overall scores at week 12 (-0.9 with lithium and -1.1 without lithium, $P < 0.0001$ for both groups). There were no statistically significant differences in clinical improvement between patients taking *Lamictal* with or without concomitant lithium. Headache, insomnia, and nausea were reported more frequently in patients receiving *Lamictal* with concomitant lithium (6%, 5%, 5%, respectively) compared to those without (5%, 3%, 3%, respectively). No serious rash was reported in the study.[195]

Ghaemi et al retrospectively reviewed charts of 21 patients (mean age, 43 years) receiving combination *Lamictal* (mean dose, 179 mg/day; range 25-500 mg/day) and lithium (mean dose, 963 mg/day; 150-2000 mg/day) as long-term treatment of refractory bipolar disorder.[196] Duration of treatment averaged 55.7 weeks. Based on the Clinical Global Impression-Bipolar Disorder-Improvement (CGI-BP) scale, acute antidepressant effects were observed in 48% of patients, acute anti-manic effects in 14%, and overall prophylactic effects in 29%. Adverse events were reported in 38% of patients; the most common were cognitive difficulty (29%), rash (9%), sedation (9%), and constipation (5%). Nearly half of patients (48%) discontinued the combination with lack of efficacy (19%) and activation of manic-like symptoms (19%) as the most common reasons.

Redmond et al retrospectively examined the efficacy and safety of *Lamictal* combined with either valproate (VPA) or lithium in 55 outpatients (mean age, 44 years; range, 18-65 years) with bipolar disorder.[197] Efficacy was assessed based on Clinical Global Impression Scale for Bipolar Disorder (CGI-BP) scores at baseline and after 3 months of combined treatment. Average doses were *Lamictal* 96 mg/day with VPA 1358 mg/day and *Lamictal* 186 mg/day with lithium 966 mg/day. Of 39 patients treated with *Lamictal* and VPA, 67% had a depression rating of 1 (very much improved) or 2 (much improved), 33% had a mania rating of 1 or 2, and 67% had overall illness severity scores of 1 or 2. Of 16 patients treated with *Lamictal* and lithium, 44% had improved depression ratings, 44% had improved mania ratings, and 62% had improved overall illness severity. Adverse events led to discontinuation of at least one part of the combination in 13% of patients taking *Lamictal* with VPA and in 31% of patients taking *Lamictal* with lithium. The most common adverse events were tremor, sedation, and hair loss. One patient taking *Lamictal* with VPA discontinued due to rash. No cases of serious rash were reported.

Bowden et al conducted a randomized, double-blind, placebo-controlled, parallel group maintenance study in 100 patients with bipolar I or II depression to compare the safety and efficacy of *Lamictal* as monotherapy compared with *Lamictal* in combination with VPA.[198] The study included an open phase (up to 8 weeks) during which all patients received the combination of *Lamictal* and VPA and maintenance phase (32 weeks). Patients were eligible for randomization to the maintenance phase if they met the following criteria for improvement for 2 consecutive weeks: 1) Montgomery-Asberg Depression Rating

Scale (MADRS) total score ≤14, 2) Mania Rating Scale (MRS) score ≤14, and 3) Global Assessment Scale (GAS) score ≥51. Dosing was not described. Preliminary data was presented from the first 57 patients in the open phase. Thirty-three (58%) patients met criteria randomization by week 8. Mean MADRS and MRS scores decreased from 26.5 and 9, respectively, at baseline to 6.2 and 4.8, respectively, at randomization. No patient developed a serious rash.

In a post-hoc analysis of the combined studies, Bowden et al compared the tolerability and effectiveness among patients receiving concomitant valproate (VPA) during the open-label phase (n = 200, 18%) to those not receiving concomitant VPA (n = 1105).[193] In the subgroup of patients receiving VPA, the mean co-exposure was 6.6 weeks. The mean doses were 54 mg/day of *Lamictal* and 1011 mg/day of VPA. Improvement in psychiatric rating scales (HAM-D, Mania Rating Scale [MRS], and global improvement scores) and incidence of adverse events were similar between the two patient groups. No cases of serious rash were reported in patients receiving concomitant VPA. No significant difference in rates of rash was observed between patients receiving VPA and those who did not (14% vs 10%, $P = 0.22$).

Another post-hoc analysis of clinical response and adverse-event profiles in patients (mean age, 42 years) treated with *Lamictal* with or without concomitant VPA was conducted from a prospective, open-label study in patients with bipolar I disorder designed to assess the rate of rash in patients with or without specific dermatological precautions.[194,195] *Lamictal* was administered alone or in combination with other medications for 12 weeks, including a 5-week titration period. Of the 1175 patients included in the study, 260 (22%) were receiving concomitant VPA. [194]Statistically significant improvement from baseline was observed with *Lamictal* with and without VPA based on mean Clinical Global Impression-Bipolar version (CGI-BP) Severity Overall scores at week 12 (-0.8 with VPA and -1.1 without VPA, $P < 0.0001$ for both groups). There were no statistically significant differences in clinical improvement between patients taking *Lamictal* with or without concomitant VPA. Tremor, rash, and dizziness were each reported by 5% of patients taking VPA and 1%, 4%, and 3% of patients not taking VPA, respectively. No serious rash was reported in the study.[195]

In a post-hoc analysis of the combined studies, Bowden et al compared the tolerability and effectiveness of *Lamictal* among patients taking concomitant atypical antipsychotics during the open-label phase (n = 196, 15%) to those not taking concomitant atypical antipsychotics (n = 1109).[193] In the subgroup of patients taking atypical antipsychotics, the mean co-exposure was 7.2 weeks. The mean doses were 106.3 mg/day of *Lamictal*, 8.5 mg/day of olanzapine, 146.5 mg/day of quetiapine, 196.4 mg/day of clozapine, and 2.9 mg/day of risperidone. Improvement in psychiatric rating scales were similar between patients who received *Lamictal* with and without atypical antipsychotics. Mean observed scores on Clinical Global Impression of Severity scale and Global Assessment Sscale improved for patients taking *Lamictal* with atypical antipsychotics from 4.5 and 46.6, respectively, at study entry to 3.2 and 61.1, respectively, at the end of the open-label phase. Adverse events were similar between patients who received *Lamictal* with and without atypical antipsychotics; the most common adverse events (>10%) were headache (18% vs 25%), all rash (8% vs 10%), infection (8% vs 11%), nausea (8% vs 12%), and dizziness (7% vs 10%). No serious rash was reported by patients taking *Lamictal* with atypical antipsychotics.

Another post-hoc analysis of clinical response and adverse-event profiles in patients (mean age, 42 years) treated with *Lamictal* with or without concomitant antipsychotic agents was conducted from a prospective, open-label study in patients with bipolar I disorder designed to assess the rate of rash in patients with or without specific dermatological precautions.[194,195] *Lamictal* was administered alone or in combination with other medications for 12 weeks, including a 5-week titration period. Of the 1175 patients included in the study, 352 (30%) were receiving concomitant antipsychotics. Quetiapine was the most commonly used antipsychotic (n = 163).[194] Statistically significant improvement from baseline was observed with *Lamictal* with and without antipsychotics based on mean Clinical Global Impression-Bipolar version (CGI-BP) Severity Overall scores at week 12 (-1.0 with antipsychotics and -1.1 without antipsychotics, $P < 0.0001$ for both groups). There were no statistically significant differences in clinical improvement between patients taking *Lamictal* with or without concomitant antipsychotics. Insomnia was reported by 4% ofpatients receiving *Lamictal* with concomitant antipsychotics compared to 3% of those without. No serious rash was reported in the study.[195]

5. EFFICACY AND SAFETY TRIALS (FDA APPROVED)

5.1 Efficacy of *Lamictal* as Adjunctive Treatment in Adult Patients with Epilepsy

Refer to Enclosed Prescribing Information.

5.2 Efficacy of *Lamictal* As Conversion to Monotherapy in the Treatment of Adults with Epilepsy

clinical trial

A dosing algorithm was designed from previous pharmacokinetic and clinical data to maintain consistent trough concentrations of lamotrigine during VPA withdrawal to minimize seizure risk and safety concerns (Table 13).[1] [9]

Table 13. Conversion from Adjunctive Therapy with VPA to Monotherapy with *Lamictal* in Patients ≥16 Years of Age [1]

Step	Lamictal	Valproate
1	Achieve a dose of 200 mg/d according to guidelines in Prescribing Information (if not already on 200 mg/d)	Maintain previous stable dose
2	Maintain at 200 mg/d	Decrease to 500 mg/d by decrements no greater than 500 mg/d per week and then maintain the dose of 500 mg/d for 1 week
3	Increase to 300 mg/d and maintain for 1 week	Simultaneously decrease to 250 mg/d and maintain for 1 week
4	Increase by 100 mg/d every week to achieve maintenance dose of 500 mg/d	Discontinue

The appropriateness of this algorithm for conversion to monotherapy with *Lamictal* from VPA monotherapy was evaluated in a multicenter open-label trial of 77 patients (≥16 years of age) with epilepsy. [9] Trough serum lamotrigine concentrations (primary endpoint), adverse events, and seizure control were assessed. The trial included 3 treatment phases: dose escalation of *Lamictal* (8 weeks), VPA withdrawal (<6 weeks), and monotherapy with *Lamictal* (4 weeks). The duration of the VPA withdrawal phase was dependent on the dose of VPA.

Of the 77 patients who received study drug, the following seizure types were predominantly reported at screening (patients may have had more than one seizure type): generalized tonic-clonic (n = 39, 51%), complex partial (n = 27, 35%), and partial with secondarily generalization (n = 23, 30%).[9]

During the VPA withdrawal phase, mean lamotrigine concentrations did not significantly differ from values at the end of the escalation phase of *Lamictal* in either population (Table 14). During the monotherapy phase of *Lamictal*, mean lamotrigine concentrations did not deviate clinically (<10%) from values at the end of the escalation phase of *Lamictal* (Table 14).

Table 14. Mean (SD) Trough Serum Concentrations of Lamotrigine (µg/mL) [199]

Phase	Mean (SD) Trough Serum Concentrations of Lamotrigine* (µg/mL)		
Monotherapy Completer Population† (n = 34)	**Pharmacokinetic Population‡ (n = 67)**	**Intent-To-Treat Population§ (n = 77)**	
Escalation of *Lamictal* (weeks 1-8)	7.0 (3.1)	7.9 (3.3)	7.9 (3.3)
VPA Withdrawal (weeks 9-14)	8.4 (3.5)	8.7 (3.5)	9.3 (5.5)
Monotherapy with *Lamictal* (weeks 15-18)	7.2 (3.3)	7.2 (3.3)	8.0 (4.1)

*Note: no therapeutic range of serum concentrations has been established for *Lamictal*

† Included patients who completed the final visit (4th week) in the monotherapy phase of *Lamictal* and followed the dosing conversion algorithm as outlined in the protocol

‡ Included patients with ≥1 serum concentration after initiation of *Lamictal* and followed the dosing conversion algorithm as outlined in the protocol

§Included patients who received ≥1 dose of *Lamictal*

Of the 57 patients that entered the monotherapy phase of *Lamictal*, 48 completed the fourth week of monotherapy treatment. [9] Of the 9 withdrawals during the monotherapy phase, 7 were due to adverse events and 2 were due to worsening of seizures. In both patients, low serum concentrations of lamotrigine were suggestive of non-compliance. The most commonly reported drug-related adverse events during the trial were dizziness (23% of patients), nausea (16%), headache (14%), tremor (13%), and asthenia (12%). Five patients reported rash that was considered related to *Lamictal*, but none met criteria for being serious. (**NOTE**: no therapeutic range of serum concentrations has been established for *Lamictal*).

controlled trial

A double-blind, double-dummy, active-control trial evaluated the use of *Lamictal* as monotherapy for the treatment of partial seizures in adults whose seizures were inadequately controlled (≥4 seizures/month) with CBZ or PHT monotherapy. [8]. Patients (n = 156, 13-73 years of age) were randomized to receive VPA 1000 mg/d or *Lamictal*. An active control (VPA) was used for ethical reasons to provide some seizure protection. The results of this trial cannot be interpreted to imply the superiority of *Lamictal* over VPA.

Following an 8-week baseline period, patients entered an 8-week transition period in which study drugs were titrated to the target doses (first 4 weeks) and PHT or CBZ were gradually discontinued (second 4 weeks). *Lamictal* was dosed as follows: days 1-3: 100 mg/d, days 4-7: 200 mg/d, days 8-14: 300 mg/d, days 15-21: 400 mg/d, and days 22 -140: 500 mg/d. **NOTE**: Titration of *Lamictal* was faster than currently recommended. Please see Prescribing Information for current dosing recommendations. Two dose reductions were permitted in the event of intolerance. The dose of VPA was increased by 250 mg/d to the target dose of 1000 mg/d (days 1-3: 500 mg/d, days 4-7: 750 mg/d, days 8-140: 1000 mg/d). After achieving target doses of *Lamictal* and VPA (500 mg/d and 1000 mg/d respectively), CBZ or PHT were withdrawn in weekly 20% decrements over 4 weeks.

Patients successfully converted to *Lamictal* or active control then entered a 12-week monotherapy period. Patients were required to withdraw from the trial after the first 4 weeks of the transition period if they met any of the following "escape" criteria: 1) doubling of average monthly seizure rate; 2) doubling of the highest consecutive 2-day seizure rate; 3) emergence of a new, more severe seizure type; or 4) clinically significant prolongation of generalized tonic-clonic seizures.

Efficacy analyses included outcomes from the protocol-specified population (n = 114) which included all patients who completed monotherapy or met escape criteria (escapers) and the intent-to-treat (ITT) population (n = 156) which consisted of all randomized patients (Table 15). A total of 42 patients (*Lamictal* n = 26, VPA n = 16) were withdrawn from the trial due to reasons other than meeting escape criteria, including protocol violations or adverse events. In the protocol-specified analysis, more than twice as many patients in the group receiving *Lamictal* successfully completed 12 weeks of monotherapy than in active control group (Table 15). Data from the intent-to-treat analysis are also shown in Table 15.

The differences in seizure-control did not appear to be related to pharmacokinetic factors since plasma concentrations of lamotrigine and VPA were similar between completers and escapers.

Table 15. Efficacy Analyses in Conversion to Monotherapy Trial [8]

	Number (%) of Completed Patients			
Analysis	**Total**	**Completed Monotherapy**	**Escaped**	**Median Time to Escape (days)**
Per Protocol				
Lamictal	50	28 (56%)*	22 (44%)	>168‡
Valproate	64	13 (20%)	51 (80%)	57
Intent-to-Treat				
Lamictal	76	28 (37%)†	32 (42%)	NA
Valproate	80	13 (16%)	55 (69%)	NA
* $P < 0.001$ †$P = 0.0012$ ‡$P = 0.001$, NA= not applicable				

Adverse events were reported more frequently for both groups of patients during the 8-week transition period (polytherapy with CBZ or PHT) than during the 12-week monotherapy period [8]. In the ITT population, the most common adverse events reported by patients receiving *Lamictal* during the monotherapy period were vomiting, headache, dizziness, nausea, dyspepsia, and coordination abnormalities (7-9%). Headache (14%) and tremor (7%) were the most common adverse events experienced by patients receiving VPA during the monotherapy period. The incidence of somnolence reported by patients during monotherapy was 0% for *Lamictal* and 2% (n = 1) for VPA. Rash occurred in 11% (n = 8) of patients receiving *Lamictal* and 8% (n = 6) of patients receiving VPA during the initial 8-week transition period; however, 2% (n = 1) of both treatment groups experienced rash during monotherapy. Rash led to hospitalization in 2 of 6 patients who discontinued *Lamictal* due to rash. One rash was diagnosed as Stevens-Johnson syndrome and both patients recovered without sequelae upon discontinuation. One patient receiving VPA discontinued due to rash. The authors acknowledged that the occurrence of rash in patients receiving *Lamictal* might have been due to the use of a higher starting dose and faster dose escalation.

5.3 Efficacy of *Lamictal* as Adjunctive Treatment of Primary Generalized Tonic-Clonic (PGTC) Seizures

Clinical Information

A multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy and tolerability of *Lamictal* as adjunctive therapy in 117 patients (2-55 years of age) with PGTC (previously known as grand mal) seizures.[6] The trial consisted of the following phases: screening (≤2 weeks), baseline (8 weeks), escalation (12 weeks for patients 2-12 years or 7 weeks for patients >12 years), and maintenance (12 weeks). Patients had ≥3 PGTC seizures during the 8-week baseline phase or based on reliable documentation for inclusion and were receiving 1 or 2 other antiepileptic drugs (AEDs) at stable doses for ≥4 weeks. Patients with partial seizures were excluded on the basis of seizure history and screening electroencephalograms (EEGs). Patients with other generalized seizure types (e.g. absence and myoclonic) in addition to PGTC seizures were enrolled in the study. Target doses for *Lamictal* are in Table 16.

Table 16. Target Doses of *Lamictal* in Biton et al Trial Based on Concomitant AED and Patient Age [6]

Dosing Regimen	Patients 2-12 years	Patients >12 years
Taking valproate	3 mg/kg/d	200 mg/d
Taking AEDs other than valproate, carbamazepine, phenytoin, phenobarbital, or primidone	6 mg/kg/d	300 mg/d
Taking carbamazepine, phenytoin, phenobarbital, and/or primidone and NOT taking valproate	12 mg/kg/d	400 mg/d
AED=antiepileptic drugs, d=day, kg=kilogram, mg=milligram		

Of 121 randomized patients, 117 (n = 58 *Lamictal*, n = 59 PBO) entered the escalation phase and 42 (72%) receiving *Lamictal* and 45 (76%) receiving PBO completed the trial. The most common concomitant AEDs were valproate (VPA), phenytoin, topiramate, carbamazepine, and phenobarbital. Mean lamotrigine

trough plasma concentrations at end of the maintenance phase were 7 mcg/mL in patients taking VPA and approximately 3 mcg/mL in patients taking other AEDs.

During the escalation and maintenance phases combined, median percent reduction in PGTC seizure frequency in the intent-to-treat population (primary endpoint) was 66% with *Lamictal* versus 34% with PBO ($P = 0.006$) (Figure 6).[6] A similar pattern of results was observed for all generalized seizures.[6] The onset of efficacy for PGTC seizures was evident within the first 2 weeks of treatment with *Lamictal* and reached statistical significance versus PBO at week 6 ($P = 0.036$) among the overall population and at week 4 among patients >12 years ($P = 0.045$).[200] In a post-hoc analysis of time to nth seizure from baseline, *Lamictal* was superior to PBO in median days to third, sixth, ninth, and twelfth seizure. ($P < 0.022$, all).[201] Median PGTC seizure counts per month also significantly decreased with *Lamictal* compared with PBO during treatment phases (0.95 with *Lamictal* versus 2.29 with PBO during escalation [$P = 0.013$] and 0.42 with *Lamictal* versus 1.61 with PBO during maintenance [$P = 0.001$]).[6] Patients with ≥25%, ≥50%, ≥75%, and 100% reductions in the frequency of PGTC and all generalized seizures during the escalation and maintenance phases combined are shown in Table 17.

Figure 6. Median Percent Reduction in Primary Generalized Tonic-Clonic Seizures[6]

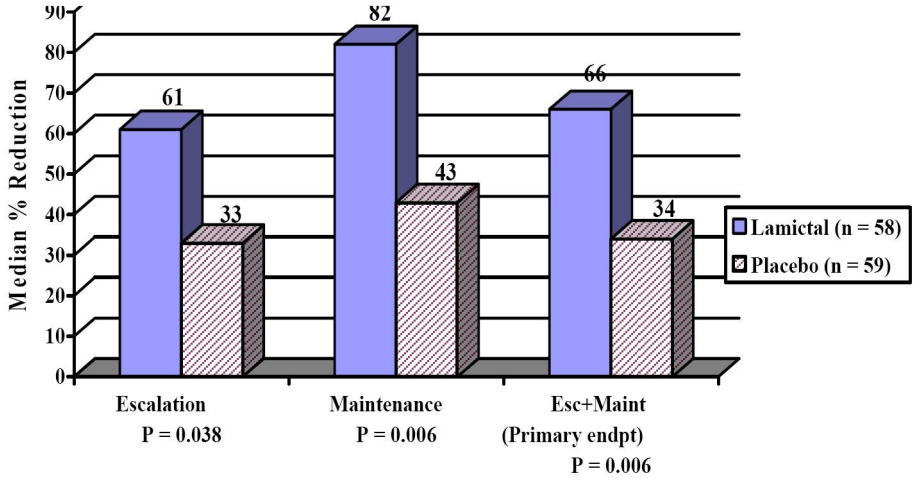


Table 17. Percent of Patients with Reductions in PGTC and all Generalized Seizures [6]

	PGTC Seizures		All Generalized Seizures	
Seizure Reduction during Escalation+Maintenance	*Lamictal* % (n = 58)	Placebo % (n = 59)	*Lamictal* % (n = 58)	Placebo % (n = 59)
≥25% Reduction	79*	54	72*	44
≥50% Reduction	64*	39	48	34
≥75% Reduction	41*	22	31*	14
100% Reduction	21	17	16	12

PGTC = primary generalized tonic clonic

*$P < 0.05$ *Lamictal* versus placebo

Efficacy did not appear to differ by age group, although sample sizes were too small for definitive conclusions (2 to 12 years [n = 12 *Lamictal* and n = 11 PBO] and >12 years [n = 46 *Lamictal* and n = 48 PBO].[6] In a post-hoc analysis of 45 children and adolescents (2-20 years) in this trial, the median percent decrease from baseline in PGTC seizures during the entire treatment period was 77% for *Lamictal* and 40% for PBO ($P = 0.044$).[202] The median percent decrease during the escalation and maintenance phases were 72% and 83% for *Lamictal* and 30% and 42% for PBO, respectively ($P = 0.059$ and $P = 0.058$). Forty-eight percent of pediatric and adolescent patients were seizure-free during the maintenance phase compared to 17% of patients receiving PBO ($P = 0.051$). Median PGTC seizure counts per month over the entire treatment period were 0.4 for *Lamictal* and 2.5 for PBO ($P = 0.007$).

The most common (≥5% in either group) drug-related adverse events in the overall study population were dizziness (5% *Lamictal*, 2% PBO), somnolence (5% *Lamictal*, 2% PBO), and nausea (5% *Lamictal*, 3% PBO).[6] Five patients receiving *Lamictal*, including one case of non-serious rash, and two receiving PBO, withdrew due to adverse events. Non-serious rash was reported by 3% of patients in both groups.[203] No serious rash was reported.[6] Body weight did not change significantly within or between groups during treatment; median weight change was 0 kg in patients receiving *Lamictal* and 0.2 kg in patients receiving PBO from baseline to the end of maintenance treatment. No patient receiving *Lamictal* prematurely withdrew from the trial because of increased frequency of myoclonic seizures.

A 52-week, multicenter, open-label continuation trial evaluated the effects of *Lamictal* on long-term safety and seizure control among 117 patients who failed baseline (n = 28) or completed the double-blind phase of this trial (n = 42 previously receiving *Lamictal* and n = 47 previously receiving PBO).[203] All three groups showed a reduction in PGTC and all generalized seizure frequency following adjunctive maintenance therapy with *Lamictal* for up to 52 weeks. Nearly half of patients (45% and 43%) continuing from the double-blind phase (previously receiving *Lamictal* and PBO) were PGTC seizure-free during long-term maintenance. The overall incidence of adverse events was similar between groups (71% of patients who failed baseline and 79% who previously received *Lamictal* or PBO). The most commonly (>10%) reported adverse events in patients who failed baseline, completed the double-blind phase receiving *Lamictal*, or completed the double-blind phase receiving PBO, respectively, were headache (21%, 29%, and 32%), dizziness (7%, 12%, and 17%), nausea (7%, 12%, and 15%), and pyrexia (7%, 10%, and 15%). Non-serious rash was reported in 3 patients (all in baseline failure or previous PBO-treated patients) and led to discontinuation in 1 patient. Serious adverse events were reported in none of the baseline failure patients, 7% of patients who previously received *Lamictal*, and 13% of previous PBO-treated patients. One fatality (reported as status epilepticus and not considered drug-related) occurred in a patient who previously received PBO. No clinically relevant effects on body weight were noted in any group during the continuation phase.

Beran et al conducted a multicenter, double-blind, placebo-controlled, crossover trial of adjunctive therapy with *Lamictal* in 26 patients (ages, 15-50 years) with treatment-resistant generalized epilepsy.[204] Seizure types included absence and tonic-clonic (n = 12); absence alone (n = 8); and absence, myoclonic, and tonic-clonic (n = 2). All patients received valproate (VPA; mean daily dose 2750 mg) either as monotherapy (n = 11) or in combination with other AEDs. The trial consisted of two 8-week treatment periods followed by a 4-week washout period. *Lamictal*, dosed 150 mg/d in patients taking VPA with an enzyme-inducing antiepileptic drug (EIAED) and 75 mg/d in patients taking VPA without an EIAED, or placebo (PBO) was added to the patient's existing regimens of ≤4 AEDs. The dose escalation was faster than currently recommended. Open-label continuation treatment was offered at the end of the trial.

Twenty-two patients completed the trial. There was a significant reduction in frequency of tonic-clonic seizures and absence seizures following treatment with *Lamictal* versus PBO ($P = 0.03$ and $P < 0.001$, respectively). Overall, a ≥50% seizure reduction was observed for tonic-clonic seizures in 50% of patients and for absence seizures in 33% of patients compared with PBO. Plasma concentrations of lamotrigine were 1.3-5.2 mg/L. Rash was the only adverse event leading to discontinuation of *Lamictal* (n = 2). Most adverse events were rated as mild to moderate. Adverse events reported in >5% during treatment with *Lamictal* and greater than PBO were rash (n = 7), ataxia (n = 3), diplopia (n = 3), dizziness (n = 2), tremor (n = 2), and drowsiness (n = 2); tiredness was reported in five patients receiving PBO versus one receiving *Lamictal*. The majority of patients (n = 23) choose to continue open-label *Lamictal*, with 20 receiving *Lamictal* for a mean of 26 months. In these 20 patients, 80% had ≥50% seizure reduction and 25% (n = 5) were seizure-free.

5.4 Efficacy of *Lamictal* as Adjunctive Therapy in Children (2 Years and Older) with Partial Seizures, Generalized Tonic-Clonic Seizures, and Generalized Seizures of Lennox-Gastaut Syndrome

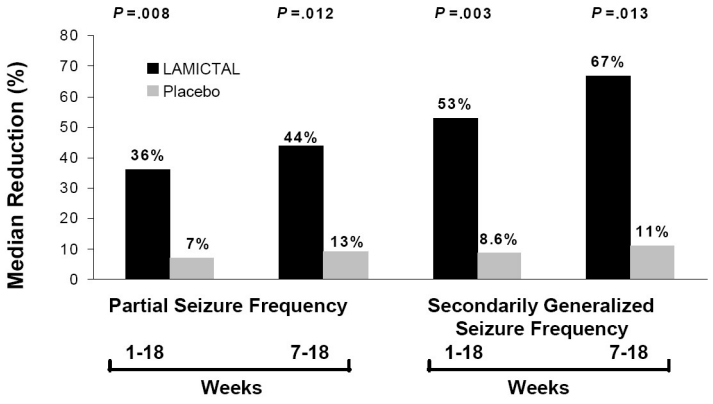
Partial seizures

The efficacy of *Lamictal Tablets* as adjunctive therapy in 199 children and adolescents (2-16 years) with partial seizures of any subtype.[5] Patients were included if they were experiencing ≥4 seizures during each of two consecutive 4-week periods during baseline while receiving a stable regimen of ≤2 AEDs, excluding felbamate (FBM) and gabapentin. The study consisted of four phases: screening, baseline (8 weeks), treatment (18 weeks: 6-week dose escalation and 12-week maintenance period), and taper and follow-up

(1 to 6 weeks, depending on treatment stage dose). Dosing of *Lamictal Tablets* was based on body weight and concomitant AEDs and ranged from 1-15 mg/kg/d with absolute maximum of 150-750 mg/d.

Patients treated with *Lamictal Tablets* experienced a statistically significant reduction in the frequency of both partial (primary endpoint) and secondarily generalized seizures compared with placebo. For the intent-to treat population, the median reduction of all partial seizures from baseline was 36% in patients treated with *Lamictal Tablets* versus 7% on placebo ($P = 0.008$) (Figure 7) . For secondarily generalized seizures, the rates were 53% versus 8.6%, respectively ($P = 0.003$). Patients receiving *Lamictal Tablets* experienced a statistically significant increase in median seizure-free days compared to placebo (28% vs. 3%, respectively)

Figure 7. Overall Improvement in Seizure Frequency from Baseline in Duchowny et al [5]



Similar numbers of patients receiving *Lamictal Tablets* (n = 92) and placebo (n = 96) reported treatment-emergent adverse event. Adverse events reported more frequently ($P < 0.05$) by patients receiving *Lamictal Tablets* compared with patients receiving placebo included dizziness (21% vs 5%), tremor (12% vs 2%), nausea (11% vs 2%), and ataxia (10% vs 2%). Adverse events leading to withdrawal included rash (n = 4) and tremor (n = 1) with *Lamictal Tablets* versus rash (n = 3), increased seizures (n = 1), brain tumor (n = 1), and threatened suicide (n = 1) with placebo. Overall, rash was reported in 16 patients on *Lamictal Tablets* and 18 patients on placebo. The authors noted that the higher dose and dose escalation of *Lamictal Tablets* may have contributed to an increased incidence of rash in this study.

Primary Generalized tonic-clonic (PGTC) seizures

A randomized, double-blind, placebo-controlled, trial evaluated the efficacy and tolerability of *Lamictal Tablets* as adjunctive therapy in patients (2-55 years) with PGTC seizures (with or without other idiopathic generalized seizure types including absence and myoclonic).[6] A post-hoc analysis was performed to evaluate *Lamictal Tablets* in a subset of children and adolescents (n = 45, 2-20 years, mean age of 11 years).[202] *Lamictal Tablets* was initiated at 0.15 to 0.6 mg/kg/d and titrated to a target of 2.7 - 12 mg/kg/d in patients aged 2-12 years. *Lamictal Tablets* was initiated at 12.5 – 50 mg/d and titrated to a target of 150 to 400 mg/d in patients aged 13-20 years old. The study consisted of 3 phases: 1) baseline; 2) escalation, during which study drug was titrated to a target dose (12 weeks for patients 2-12 years, 7 weeks for patients >12 years); 3) maintenance, during which doses of study drug and concomitant AEDs were maintained for 12 weeks.

The results from the overall study population were statistically significant, however, the study was not powered to evaluate pediatric patients. For patients 2-20 years, the median percent decrease from baseline in PGTC seizures (primary endpoint) during the entire treatment period was 77% for *Lamictal Tablets* and 40% for PBO ($P = 0.044$, Figure 8). Median PGTC seizure counts per months are shown in Figure 9. During the maintenance phase, 48% of patients receiving *Lamictal Tablets* were PGTC seizure-free compared to 17% receiving PBO, respectively ($P = 0.051$).

Figure 8. Median % Decrease in PGTC Seizures [202]

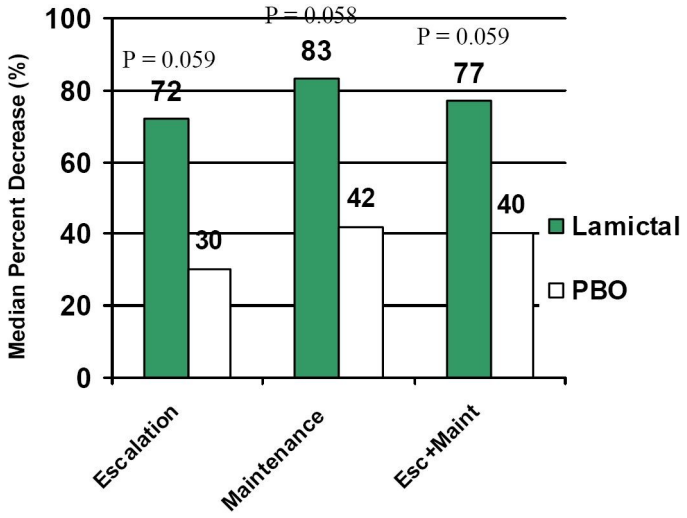
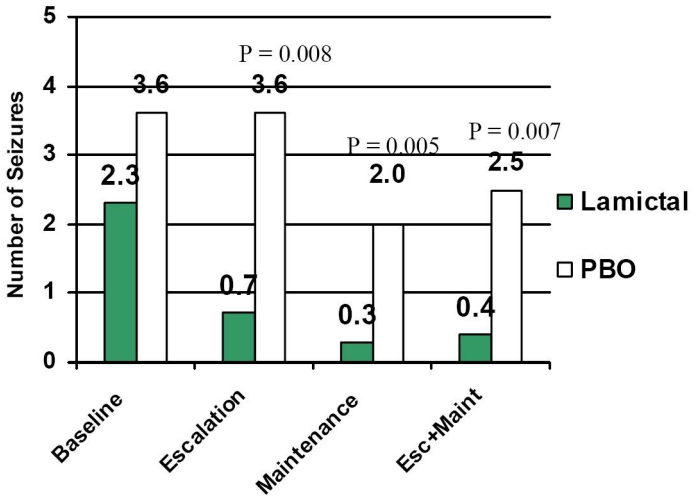


Figure 9. Median PGTC Seizure Count per Month [202]



The most common (≥10%) treatment-emergent adverse events for *Lamictal Tablets* versus PBO were headache (10% vs. 25%), nasopharyngitis (14% vs. 4%), and convulsion (10% vs 17%). One patient from each treatment group discontinued from the study because of an adverse event. No rashes occurred among patients in either group. No patient experienced worsening of myoclonus.

Generalized Seizures of Lennox-Gastaut syndrome (LGS)

Motte et al investigated the use of *Lamictal Tablets* as adjunctive therapy in LGS in a double-blind, placebo-controlled trial in 169 patients (3-25 years). [7] Eligible patients had ≥1 type of predominantly generalized seizure (including tonic-clonic, atonic, tonic, and major myoclonic) at a frequency of ≥1 seizure every other day for ≥1 year. Patients were randomized to 16 weeks of treatment with *Lamictal Tablets* (n = 79) or placebo (n = 90) added to their current antiepileptic regimen of ≤3 drugs. Patients received a fixed-dose of *Lamictal Tablets* titrated over six weeks up to 5.0 mg/kg/d (maximum dose 200 mg/d) for patients taking valproate (VPA) and 15.0 mg/kg/d (maximum dose 400 mg/d) for patients not taking VPA. The primary efficacy endpoint was percent change from baseline in the frequency of major motor seizures during treatment weeks 1 - 16.

Baseline characteristics were similar between groups, with the exception that significantly more males were in the *Lamictal Tablets* group (*P* = 0.02). Approximately 91% of patients in each group had moderate or

severe intellectual impairment. Median weekly seizure counts for all major seizures were reduced by 32% in patients treated with *Lamictal Tablets* and 9% in patients taking placebo ($P = 0.002$). Drop attacks and tonic-clonic seizures in patients taking *Lamictal Tablets* were significantly reduced compared with placebo ($P < 0.05$). The change from baseline of atypical absence seizures were not significantly different between groups. Significantly more patients taking *Lamictal Tablets* experienced ≥50% reduction in the frequency of all major seizures, drop attacks, and tonic-clonic seizures compared to patients taking placebo ($P < 0.05$). Parent/care giver evaluations showed a greater improvement in general health for patients receiving *Lamictal Tablets* compared to placebo (73% vs 50%). Quality of life measures showed improvement in mood for patients receiving *Lamictal Tablets*. *Lamictal Tablets* did not alter plasma concentrations of any concomitant AED. At treatment week 16, there did not appear to be any correlation between plasma concentration and efficacy. Neurologic examinations showed significant improvements for patients treated with *Lamictal Tablets* compared with patients receiving placebo in behavior (30% vs. 14%), speech (11% vs. 2%), nonverbal communication (11% vs. 8%), and gross coordination (5% vs. 4%).[205]

Colds and viral illnesses were the only adverse events reported more frequently in patients treated with *Lamictal Tablets* than in placebo-treated patients. [7] The occurrence of rash was similar for *Lamictal Tablets* (9%, n = 7) and placebo (7%, n = 6). Rash led to study withdrawal in two patients receiving *Lamictal Tablets* and one receiving placebo.

5.5 Efficacy of *Lamictal* as Maintenance Treatment of Bipolar I Disorder in Adults

Currently or recently Manic and hypomanic patients (maintenance trial M)

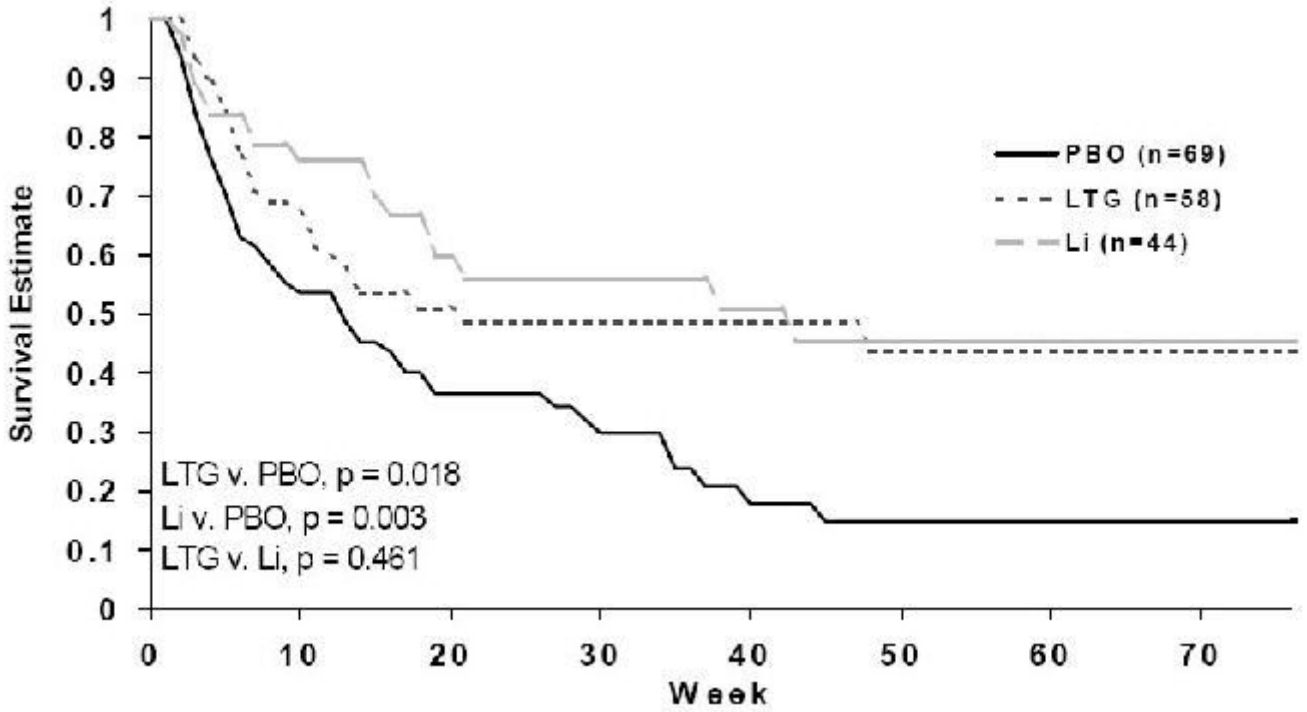
A multicenter, double-blind, placebo-controlled, 18-month study assessed the efficacy and tolerability of *Lamictal Tablets* and lithium compared with placebo (PBO) for delaying relapse or recurrence of mood episodes in currently or recently (within 60 days) manic or hypomanic adult patients with bipolar I disorder.[10] Patient demographics included: mean age of 40.7 years, 46% with history of psychotic episodes, 66% with history of prior psychiatric hospitalization, 29% with history of suicide attempts, 28% met criteria for rapid cycling (4-6 cycles per year), and 94% had more than one prior trial of psychiatric medication.

During the 8-16 week open-label phase, *Lamictal Tablets* was initiated based on concomitant valproate (VPA) or carbamazepine (CBZ) treatment or as monotherapy, titrated to a target dose, and concomitant psychotropic medications were gradually withdrawn. Dose escalation followed the recommendations in the Prescribing Information for *Lamictal Tablets*. Patients with a CGI-severity score of ≤3 and maintained for ≥4 continuous weeks, including at least the final week on monotherapy with *Lamictal Tablets*, were randomized to a placebo-controlled, double-blind treatment period for up to 18 months. Psychotropic medications, other than study medication and short-term use of chloral hydrate and low-dose benzodiazepines, were not allowed during the double-blind phase. The primary endpoint, time to intervention for any mood episode (depression, mania, hypomania, or a mixed) or one that was emerging (TIME), included the time from randomization to intervention with additional pharmacotherapy or electroconvulsive therapy (ECT).

Of 349 patients meeting screening criteria and entering the open-label phase, 175 (50%) met stabilization criteria and were randomized to double-blind maintenance treatment (*Lamictal Tablets* 100-400 mg/day [d] with starting dose of 200 mg/d, n = 59; lithium 0.8-1.1 mEq/L, n = 46; and PBO n = 70). The protocol was amended to discontinue enrollment into the lithium group due to administrative reasons. Therefore, the lithium arm was under-powered relative to PBO and *Lamictal Tablets* and results should be interpreted accordingly. In addition, because the study was terminated before enrollment was complete, all study arms were under-powered from their original estimated sample sizes (n = 110 per group).

The mean dose of *Lamictal Tablets* was ~211 mg/d. Both *Lamictal Tablets* and lithium were superior to PBO at prolonging TIME ($P = 0.018$ *Lamictal Tablets* versus PBO; $P = 0.003$ lithium versus PBO; Figure 10). [10] *Lamictal Tablets* was also superior to PBO on overall survival in study (TIME plus discontinuation for any reason, $P = 0.03$) and at prolonging time to a depressive episode ($P = 0.015$). Patients receiving *Lamictal Tablets* remained intervention-free for a mood episode for a median of 141 days versus 85 days for patients receiving PBO. There were no significant differences between *Lamictal Tablets* and lithium on efficacy measures.

Figure 10. Time to Intervention for a Mood Episode in Maintenance Trial M [10]



The number of patients in each treatment group who ever had a score of ≥3 on the Hamilton Rating Scale for Depression (HAM-D), item 3 (suicidality) during the double-blind phase did not differ significantly between treatment groups (*Lamictal Tablets* n = 2, lithium n = 0, PBO n = 2).[10] The most frequent adverse events leading to withdrawal during the open-label phase were rash (n = 17, 5%) and mania (n = 12, 3%). There was one report of serious rash during the open-label phase and none during the double-blind phase. During the double-blind phase, headache was reported at a significantly higher rate in patients receiving *Lamictal Tablets* versus lithium (20% vs 4%, *P* = 0.02; PBO 16%) and diarrhea was reported at a significantly higher rate in patients receiving lithium versus *Lamictal Tablets* and PBO (28% vs 5% and 9%; *P* = 0.002).

Currently or Recently Depressed Patients (Maintenance Trial D)

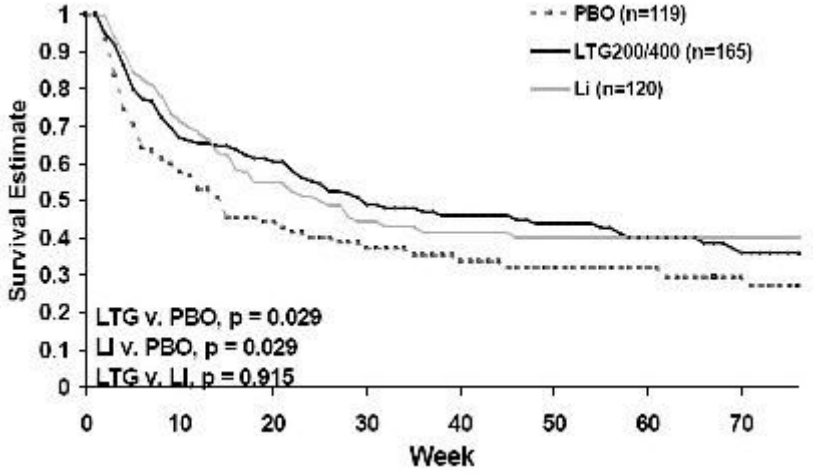
Long-term mood stabilization was evaluated in 966 currently or recently (within 60 days) depressed outpatients (≥18 years) with bipolar I disorder in a multicenter, randomized, double-blind trial similar to Maintenance Trial M.[10,11] Patient demographics included: mean age of 42.2 years, 66% with history of prior psychiatric hospitalization, and 37% with history of suicide attempts. During the 8-16 week open-label stabilization phase, patients received *Lamictal Tablets* as monotherapy or add-on to other psychotropic medications.

Following the open-label stabilization phase (n = 463), patients meeting stabilization criteria were randomized to double-blind monotherapy with *Lamictal Tablets* (fixed doses of 50, 200, or 400 mg/d, n = 221), lithium (0.8-1.1 mEq/L, n = 121), or PBO (n = 121) as maintenance for up to 18 months. Prior to patient enrollment, an a priori decision was made to combine the existing 200 and 400 mg/d groups for the primary analysis of efficacy. To facilitate patient enrollment, the protocol was amended to stop enrollment in the 50 and 400 mg/d groups.

Both *Lamictal Tablets* and lithium were superior to PBO at delaying TIME, the primary endpoint (*P* = 0.029 both *Lamictal Tablets* and lithium vs PBO) (Figure 11). Patients receiving *Lamictal Tablets* remained intervention-free for a mood episode for a median of 200 days versus 93 days for patients receiving PBO. Among patients experiencing mood episodes, interventions for emerging symptoms of depression outnumbered interventions for manic symptoms by nearly 3:1. *Lamictal Tablets* was also superior to PBO on overall survival in study (*P* = 0.003) and at prolonging time to a depressive episode (*P* = 0.047). There were no significant differences between *Lamictal Tablets* and lithium on efficacy

measures. Separate analyses of the 200 and 400 mg/d dose groups revealed no added benefit from the higher dose. Neither the 50 mg/d (n = 50) nor the 400 mg/d (n = 45) dose groups differed significantly from PBO on delaying TIME or overall survival in study (TIME: *P* = 0.634, *P* = 0.571; survival in study: *P* 0.059, *P* = .274, respectively).

Figure 11. Time to Intervention for a Mood Episode in Maintenance Trial D [11]



The number of patients in each treatment group who ever had a score of ≥3 on HAM-D, item 3 (suicidality) during the double-blind phase did not differ significantly between groups (*Lamictal Tablets* n = 3, lithium n = 2, PBO n = 1).[11] The most common adverse events leading to withdrawal during the double-blind phase for PBO, lithium, and *Lamictal Tablets*, respectively were: nausea (2%, 7%, 1%), tremor (2%, 6%, 1%), dizziness (2%, 4%, 0%), and non-serious rash (1%, 1%, and 4%). Any rash was reported at a significantly higher rate in patients receiving *Lamictal Tablets* versus PBO (7% vs 2%; 4% lithium) during the double-blind phase. There was one report of serious rash during the open-label phase.

Combined analysis of Currently or recently depressed, Manic, or hypomanic patients

The two previous controlled maintenance studies were prospectively designed to be combined for a more highly powered assessment of the main treatment effects of *Lamictal Tablets* and lithium and their relative efficacy on manic and depressive episodes, specifically. [12] Currently or recently symptomatic bipolar I patients (N = 1315) were enrolled and received *Lamictal Tablets* during the 8-16 week open-label phase. Approximately half of patients (n = 638) were stabilized and randomized for up to 18 months of double-blind monotherapy with *Lamictal Tablets* (n = 280; 50-400 mg/d at fixed or flexible doses), lithium (n = 167; titrated to 0.8-1.1 mEq/L) or PBO (n = 191). The overall demographics and disease characteristics were comparable across double-blind treatment groups and indicative of moderate severity of illness. The primary endpoint was TIME and secondary endpoints included time to intervention for depression, time to intervention for mania, survival in study, and tolerability.

The mean dose of *Lamictal Tablets* was 245 mg/d and the mean serum lithium level was 0.7 mEq/L. Both *Lamictal Tablets* and lithium significantly delayed TIME and overall survival in study versus PBO (TIME: *P* < 0.001 for both; survival in study: *P* < 0.001 *Lamictal Tablets* versus PBO, *P* = 0.006 lithium versus PBO). The median times to treatment intervention for mood episodes were 86 days for PBO, 184 days for lithium, and 197 days for *Lamictal Tablets* (*P* < 0.05 for *Lamictal Tablets* and lithium vs PBO). An evaluation of time to the occurrence of depression or mania revealed a statistically significant benefit for *Lamictal Tablets* over PBO in delaying the time to occurrence of both depression (*P* = 0.009) and mania (*P* = 0.034), although the finding was more robust for depression (Figure 12, Figure 13). Within the subpopulation of enrolled rapid cyclers (4-6 episodes in the past year; n = 169), TIME did not significantly differ between treatment groups, although both *Lamictal Tablets* and lithium were associated with greater improvements in survival in study versus PBO (*P* = 0.077). Mean HAMD-17 scores (LOCF) were significantly lower in patients receiving *Lamictal Tablets* versus PBO (*P* = 0.027) during the randomized phase.[206,207]

Figure 12. Time to Intervention for Depression from Combined Analysis of Maintenance Trials M and D [12]

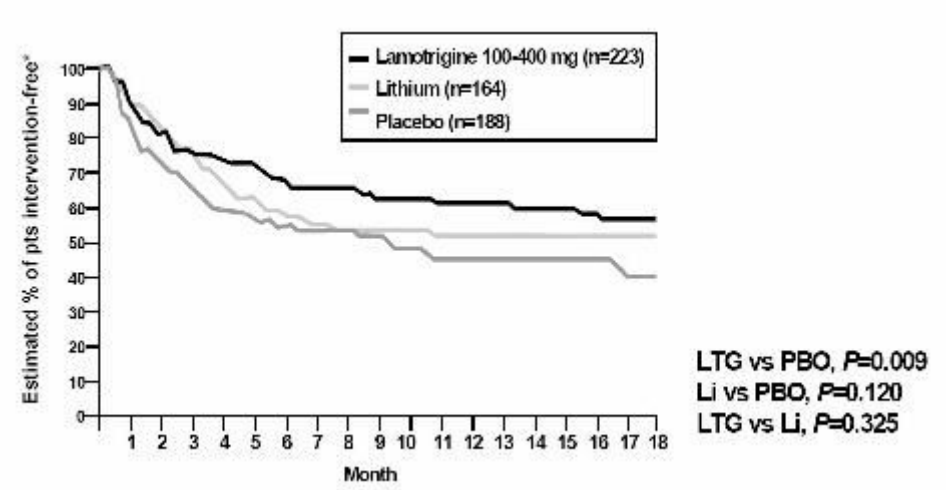
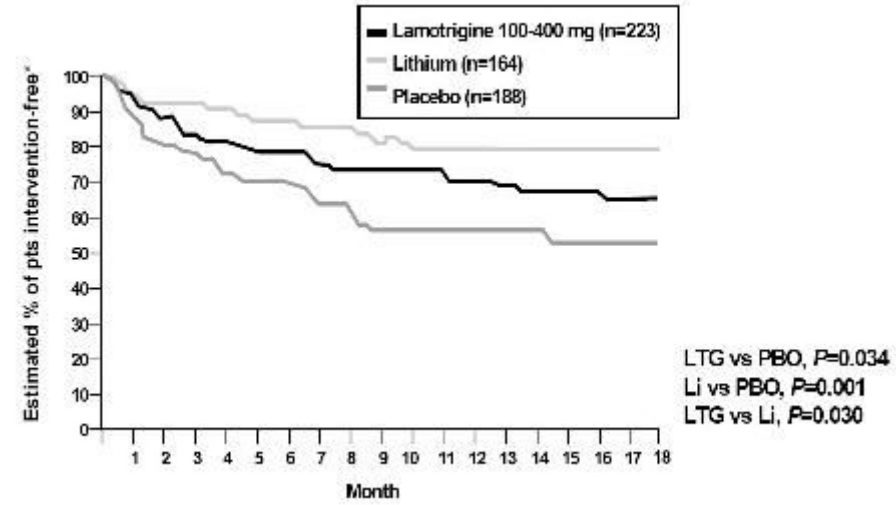


Figure 13. Time to Intervention for Mania/Hypomania from Combined Analysis of Maintenance Trials M and D [12]



The most common adverse events are reported in Table 18. [12] Discontinuation rates due to adverse events were 13% for *Lamictal Tablets*, 23% for lithium, and 16% for PBO. The rate of manic or hypomanic or mixed mood episodes reported as adverse events in these studies was 5% for *Lamictal Tablets*, 4% for lithium, and 7% for PBO.

Table 18. Common Adverse Events (≥10%) in Combined Analysis of Maintenance Trials M and D [12]

Adverse Event	Open-Label Phase (n = 1305)**	Double-Blind Phase		
		Placebo (n = 190)	Lithium (n = 166)	*Lamictal Tablets* 100-400 mg/d (n = 227)
Headache	25%	19%	15%	19%
Nausea	12%	11%	20%*	14%
Infection	11%	13%	13%	13%
Any rash‡	11%	5%	5%	7%
Dizziness	10%	9%	8%	7%
Somnolence	9%	7%	13%*	9%
Diarrhea	8%	8%	19%*†	7%
Insomnia	8%	6%	10%	10%
Tremor	4%	5%	15%*†	4%

* $P < 0.05$ lithium vs PBO; † $P < 0.05$ *Lamictal Tablets* vs lithium; ‡ There were 2 reports of serious rash during open-label phase and none during double-blind phase. Both cases resolved following discontinuation of *Lamictal Tablets*; ** 1315 patients enrolled in open-label phases; however, 10 did not continue or had incomplete data and were not included in the analysis.

6. ADDITIONAL SAFETY INFORMATION

6.1 Dermatologic Effects

Refer to Enclosed Prescribing Information.

SERIOUS RASHES REQUIRING HOSPITALIZATION AND DISCONTINUATION OF TREATMENT HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF LAMICTAL. THE INCIDENCE OF THESE RASHES, WHICH HAVE INCLUDED STEVENS JOHNSON SYNDROME, IS APPROXIMATELY 0.8% (8 PER 1,000) IN PEDIATRIC PATIENTS (AGE <16 YEARS) RECEIVING LAMICTAL AS ADJUNCTIVE THERAPY FOR EPILEPSY AND 0.3% (3 PER 1,000) IN ADULTS ON ADJUNCTIVE THERAPY FOR EPILEPSY. IN CLINICAL TRIALS OF BIPOLAR AND OTHER MOOD DISORDERS, THE RATE OF SERIOUS RASH WAS 0.08% (0.8 PER 1,000) IN ADULT PATIENTS RECEIVING LAMICTAL AS INITIAL MONOTHERAPY AND 0.13% (1.3 PER 1,000) IN ADULT PATIENTS RECEIVING LAMICTAL AS ADJUNCTIVE THERAPY. IN A PROSPECTIVELY FOLLOWED COHORT OF 1,983 PEDIATRIC PATIENTS WITH EPILEPSY TAKING ADJUNCTIVE LAMICTAL, THERE WAS 1 RASH-RELATED DEATH. IN WORLDWIDE POSTMARKETING EXPERIENCE, RARE CASES OF TOXIC EPIDERMAL NECROLYSIS AND/OR RASH RELATED DEATH HAVE BEEN REPORTED IN ADULT AND PEDIATRIC PATIENTS, BUT THEIR NUMBERS ARE TOO FEW TO PERMIT A PRECISE ESTIMATE OF THE RATE.

OTHER THAN AGE, THERE ARE AS YET NO FACTORS IDENTIFIED THAT ARE KNOWN TO PREDICT THE RISK OF OCCURRENCE OR THE SEVERITY OF RASH ASSOCIATED WITH LAMICTAL. THERE ARE SUGGESTIONS, YET TO BE PROVEN, THAT THE RISK OF RASH MAY ALSO BE INCREASED BY (1) COADMINISTRATION OF LAMICTAL WITH VALPROATE (INCLUDES VALPROIC ACID AND DIVALPROEX SODIUM), (2) EXCEEDING THE RECOMMENDED INITIAL DOSE OF LAMICTAL, OR (3) EXCEEDING THE RECOMMENDED DOSE ESCALATION FOR LAMICTAL. HOWEVER, CASES HAVE BEEN REPORTED IN THE ABSENCE OF THESE FACTORS.

NEARLY ALL CASES OF LIFE THREATENING RASHES ASSOCIATED WITH LAMICTAL HAVE OCCURRED WITHIN 2 TO 8 WEEKS OF TREATMENT INITIATION. HOWEVER, ISOLATED CASES HAVE BEEN REPORTED AFTER PROLONGED TREATMENT (e.g., 6 MONTHS). ACCORDINGLY, DURATION OF THERAPY CANNOT BE RELIED UPON AS A MEANS TO PREDICT THE POTENTIAL RISK HERALDED BY THE FIRST APPEARANCE OF A RASH.

ALTHOUGH BENIGN RASHES ALSO OCCUR WITH LAMICTAL, IT IS NOT POSSIBLE TO PREDICT RELIABLY WHICH RASHES WILL PROVE TO BE SERIOUS OR LIFE THREATENING. ACCORDINGLY, LAMICTAL SHOULD ORDINARILY BE DISCONTINUED AT THE FIRST SIGN OF RASH, UNLESS THE RASH IS CLEARLY NOT DRUG RELATED. DISCONTINUATION OF TREATMENT MAY NOT PREVENT A RASH FROM BECOMING LIFE THREATENING OR PERMANENTLY DISABLING OR DISFIGURING.

Risk Factors for Rash

Coadministration with Valproate: Risk of Rash

Messenheimer et al conducted a retrospective safety review of 68 completed safety and efficacy epilespy trials in which *Lamictal* was used as adjunctive or monotherapy in patients >12 years of age with epilepsy (N = 3514).[208] Effect of coadministration of antiepileptic agents was evaluated in adult patients (>16 years; n = 3387) as a possible risk factor for rash. The highest rate of "all rash", rash leading to discontinuation (DC), and rash associated with hospitalization occurred when *Lamictal* was coadministered with valproate (VPA) alone (19.5%, 12.2%, and 2.0% of 205 patients, respectively). In contrast, all rates were lower when *Lamictal* was administered with VPA and an enzyme inducing anticonvulsant in combination (7.6%, 3.3%, and 0.7% of 303 patients, respectively) and as monotherapy (14.5%, 6.0%, and 0% of 420 patients, respectively).

exceeding recommended initial dose and dose escalation

Messenheimer et al conducted a retrospective safety review of 68 completed safety and efficacy epilespy trials in which *Lamictal* was used as adjunctive or monotherapy in patients >12 years of age (N=3514).[208] A comparison of mean doses of *Lamictal* in the first week of treatment was conducted to evaluate dosing regimen as a risk factor. "All rash" reported with *Lamictal* as monotherapy was lowest (6.1% of 213 patients) when initiated at currently recommended initial doses of 25 mg/day compared to higher doses (20.5% - 25.4%). Rash leading to DC was reported in 1.9% of 213 patients initiating *Lamictal* as monotherapy at currently recommended doses, compared to 9.0% to 12% of patients initiated at higher doses. The highest rate of rash leading to discontinuation (DC; 13.8% of 80 patients) occurred when *Lamictal*, initiated at higher than currently recommended doses, was administered with VPA. Similar trends were observed when comparing rates of discontinuation due to rash with mean doses of *Lamictal* during the first 5 weeks of dose escalation.

Wong et al conducted a retrospective review in five tertiary epilepsy referral centers in the UK to determine the incidences of serious and nonserious rash associated with *Lamictal* (primarily in adults), the risk factors for rash, and to evaluate the impact of the manufacturer's recommendation to reduce the starting dose of *Lamictal* after January 1994. [209,210] Starting doses decreased from 50 mg/d to 25 mg every other day in patients taking VPA and from 100 mg/d to 50 mg/d in patients taking carbamazepine (CBZ), phenytoin (PHT), phenobarbital, or primidone. Serious rashes included those rashes associated with systemic involvement, including hematologic/hepatic function test abnormalities, angioedema, erythema multiforme, and SJS (Stevens Johnson syndrome; ≥2 mucosal surfaces involved).[210]

Of 2052 patients identified, 1002 were excluded due to unknown earlier dosage schedules and clinical details of the rash. Of the remaining 1050 patients, 86 (8.2%) was classified as having "possible" or "likely" dermatologic events due to *Lamictal* as classified by the World Health Organization's (WHO) criteria. Twelve cases were considered serious (1.1%) and 74 as non-serious (7%). The rate of serious rash changed from 1.5% (12/805, 2 cases of SJS) to 0% (0/245) following the recommended change in starting dose. There was no change in the total incidence of non-serious rash, with 8% (63/805) before and 9% (23/245) after the recommended dose change. The mean daily starting dose of *Lamictal* was 57.4 mg in patients who developed a rash and 49.4 mg in patients who did not develop a rash. The overall incidences of serious and non-serious rash were 4.8%, 11.0%, and 9.9% for starting doses of ≤25 mg, 25-50 mg, and >50 mg/d, respectively. Females were more likely to develop a rash associated with *Lamictal* compared with males (relative risk = 1.83). Of the 12 cases of serious rash, 10 patients were females, 11 were receiving VPA, and the mean age was 24.8 years.

Cross-sensitivity with other medications

In patients with a history of allergy or rash to other antiepileptic drugs, the frequency of nonserious rash after treatment with *Lamictal* was approximately 3 times higher in these patients than in those without such history. (211,212)

Hirsch et al retrospectively evaluated 988 outpatients with epilepsy who received *Lamictal* to determine the incidence and risk factors for rash by univariate analysis. (211) Overall, 5.7% of patients developed rash attributed to *Lamictal* and 3.9% discontinued *Lamictal* due to rash; there were no cases of TEN or hospitalizations due to rash. One patient was diagnosed with mild Stevens Johnson syndrome (SJS). Thirteen patients had a history of an immune disorder (e.g. systemic lupus erythematosus), but none experienced rash with *Lamictal*. History of rash after another antiepileptic drug (AED) was the strongest predictor of lamotrigine-associated rash (13.9% vs 4.6%, $P < 0.001$). In examining cross-sensitivity to AEDs by age, 18.2% of children and 3% of adults with a rash attributed to another AED experienced lamotrigine-associated rash. Nine of 48 patients (18.8%) with a history of rash from carbamazepine (CBZ) experienced lamotrigine-associated rash and 3/11 (27.3%) patients with a rash from oxcarbazepine (OXC) experienced lamotrigine-associated rash (both $P < 0.01$). Patients with rash from phenytoin (PHT), penicillin, and sulfa drugs were more likely to experience rash with *Lamictal*, but the number of patients in each subcategory were too small to demonstrate significance. A subsequent analysis evaluated 1037 adult outpatients (mean age 44 years) with epilepsy who received *Lamictal* (mean dose 398 mg/day) to determine the incidence and risk factors for rash by univariate analysis.(213) Overall, 4.8% of patients developed rash attributed to *Lamictal* and approximately 3.5% discontinued *Lamictal* due to rash; there were no cases of TEN . One patient was diagnosed with Stevens Johnson syndrome (SJS) and was hospitalized. The relative risk of rash for *Lamictal* in patients with a history of rash after another antiepileptic drug (AED) was 4.1 (14.4% with other AED rash vs 3.5% without other AED rash).

In a prospective, observational study that measured the frequency of neurologist reported serious and non-serious adverse events leading to interruption or discontinuation of *Lamictal* in adult patients (N = 767), patients who had a history of allergy to any drug or an AED had a 2.8-fold and 3.8-fold increased risk of discontinuation of *Lamictal* due to a rash, respectively.(212)

Alvestad et al retrospectively investigated cross-sensitivity in 663 patients with epilepsy comprising 2567 exposures to AEDs. (214) Skin reactions occurred in 93 patients, and in 18 cases were associated with ≥1 AED. In examining cross-sensitivity between *Lamictal* and PHT, CBZ, or OXC; only rash rates with *Lamictal*/PHT were statistically significant ($P = 0.03$). Three of 11 patients (27%) with a prior rash associated with PHT also exposed to *Lamictal* developed rash ($P = 0.03$). Whereas, 4/31 patients (13%; P = NS) with CBZ-associated rash and 2/9 patients (22%; $P = 0.04$) with OXC-associated rash also exposed to*Lamictal* developed rash.

Following dermatology precautions

In a randomized, 12-week study, outpatients (N = 1,175; aged ≥13 years, mean age 42 years) with bipolar I disorder were randomized to receive open-label treatment with *Lamictal* in addition to either blinded usual-care precautions (UCP; precautions for reducing the risk of rash, from the patient instructions in the Prescribing Information) or dermatology precautions (DP; UCP plus precautions in Table 19). (195) *Lamictal* was titrated according to the Prescribing Information and adjusted for concomitant medications to a target dose of 200 mg/d. The most common (>10%) concomitant psychiatric medications were bupropion, lithium, quetiapine, valproate (VPA), citalopram, and clonazepam.

Table 19. Dermatology Precautions (195) (215)

· Avoid new medicines, foods, cosmetics, conditioners, deodorants, detergents, or fabric softeners.
· Avoid sunburn and poison ivy/oak exposure.
· Do not start *Lamictal* within 2 weeks of having a vaccination, rash*, or viral syndrome.
* Specified in Ketter et al 2005, but not larger study by Ketter et al 2006

A total of 867 patients (74%) completed the study. Reasons for premature withdrawal were similar between the groups. No serious rashes were reported. Rates of non-serious rash were 50/584 (8.6%) and 52/591 (8.8%) in the DP and UCP groups, respectively (primary endpoint, $P = 0.486$). Non-serious rash led to discontinuation in 62 (5.3%) patients. Non-serious rash included the adverse event verbatim terms:

rash, bullous dermatitis, erythema, heat rash, erythematous, macular, maculo-papular, papular, pruritic and pustular rash, and urticaria. When compared to the total population, the rate of non-serious rash was similar and slightly lower in adolescent patients (1/14 [7.1%] UCP and 2/26 [7.7%] DP) and slightly higher in elderly patients (4/24 [16.7%] UCP and 1/25 [4%] DP). Adverse events (other than rash) reported in ≥5% of patients during the treatment period were headache, insomnia, dizziness, and nausea. One serious adverse event (mania) was thought to be related to *Lamictal*.

Ketter et al initially assessed the incidence of rash associated with *Lamictal* when using dermatology precautions and slower than recommended titration in an open-label study of patients (N = 100, mean age 41 years) with bipolar disorder. [215] Patients were instructed to follow the Stanford Dermatology Precautions (Table 19) for the first 3 months of treatment with *Lamictal*. In patients not taking enzyme inducers or inhibitors, *Lamictal* was initiated at 25 mg/d for 2 weeks, increased to 50 mg/d for 2 weeks, and thereafter increased by 25 mg/d per week. Doses were halved in patients taking valproate (VPA) and doubled in patients taking carbamazepine (CBZ).

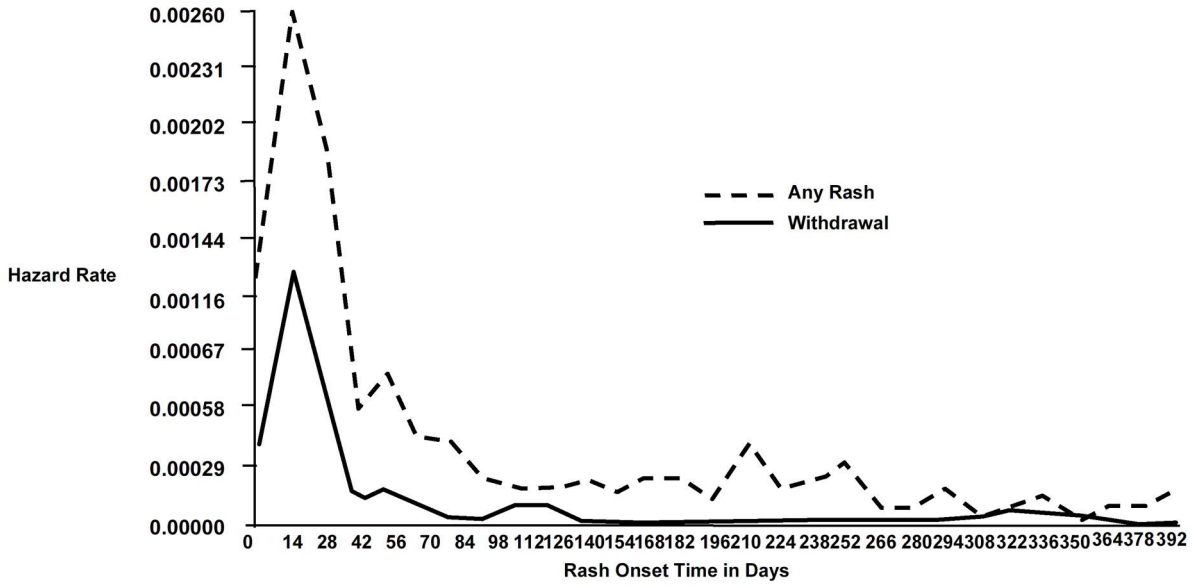
Among the 89 completers, mean final doses of *Lamictal* were 94 mg/d in patients taking VPA and 178 mg/d in patients not taking VPA. In addition to *Lamictal*, patients were taking a mean of 2.2 other psychotropic medications. Thirty-six patients had a history of immunologic and dermatologic reactions including prior drug allergies/rashes (n = 22), environmental allergies (n = 6) and eczema (n = 6). No serious rashes were reported. Nonserious rash was reported in 5 patients (5%) and resolved in 3 patients who discontinued *Lamictal* and 2 who continued *Lamictal*. Two patients with rash were found to be non-compliant with the dermatology precautions.

Timing for Appearance of Rash

Clinical Information

Isolated cases of life threatening rash associated with *Lamictal Tablets* have been reported after prolonged treatment (e.g., 6 months).[208]Figure 14 , based on Phase II and III clinical trials of *Lamictal Tablets*, depicts the hazard rate over time for any rash and rash leading to withdrawal of *Lamictal Tablets*. Accordingly, duration of therapy cannot be relied upon as a means to predict the potential risk heralded by the first appearance of a rash.

Figure 14. Hazard Plot for Any Rash and Rash Leading to Withdrawal of *Lamictal* From Phase II and III Clinical Trial Data [208]



Data from an academically based registry in Germany found that, among new users of antiepileptic drugs, more than 90% of Stevens-Johnson syndrome and toxic epidermal necrosis cases occurred in the first 63 days. [216]

A retrospective chart review evaluated timing and cause of late-onset rash (occurring ≥6 months after treatment initiation) associated with *Lamictal Tablets* in 8 patients with epilepsy.[217] According to preliminary results, the time to onset of rash from initiation of *Lamictal Tablets* as monotherapy (n = 5) or adjunctive therapy (n = 3; phenytoin, topiramate, and gabapentin) ranged from 6 to 71 months. In all of the cases, rash was determined to be caused by something other than *Lamictal Tablets* with common causes including eczema and cosmetic reaction.

Management of Rash

Among numerous published reports of serious rash (including Stevens Johnson syndrome and toxic epidermal necrosis) in adult and pediatric patients, additional treatment approaches included withdrawal of carbamazepine or valproate; supportive care; local skin treatments; and administration of intravenous (IV), oral, and/or topical corticosteroids, cyclosporine, IV immunoglobulins, antihistamines, antibiotics, fluconazole, and proton pump inhibitors. [5] [218] [219] [220] [221] [222] [223] [224] [225] [226] [227] [228] [229] [230] [231] [232,233,234,235,236] [237] [238] In these cases following onset, the duration of serious rash associated with the use of *Lamictal Tablets* varied and may have been dependent on factors such as severity of presentation and time to effective treatment. *Lamictal Tablets* was reportedly discontinued in almost all cases.

Data Reported from the German Rash Registry

Epidemiologic Data on the Incidence of Rash Associated with *Lamictal Tablets*

A registry for all serious cutaneous reactions has existed in Western Germany since 1990 and since 1996 for all of Germany. [216,239] This is an academically based registry and intensive reporting system that regularly contacts 100% of burn units, departments of pediatrics, departments of dermatology, and all internal medicine departments in hospitals with intensive care facilities or with more than 200 beds. As a result of this program, almost all cases of Stevens Johnson syndrome (SJS) and toxic epidermal necrosis (TEN) are detected prospectively and confirmed by expert review. Furthermore, the registry routinely sends letters to all relevant units to retrospectively determine if cases have been overlooked.

During the last six months of 1993, when *Lamictal Tablets* was first marketed in Germany, there were five cases of SJS or TEN associated with *Lamictal Tablets* reported in the estimated 6,100 adult patients exposed to *Lamictal Tablets* at that time (Table 20). Four patients were also receiving valproate (VPA). In the third quarter of 1993, GlaxoSmithKline amended the dosing regimen (starting dose when used with VPA was reduced from 50 mg daily to 25 mg every other day) and physicians were educated accordingly. See Table 20 and Figure 15 for rates of SJS/TEN through 2005 in adults and pediatric (<12 years) patients. In 2005, generic lamotrigine became available in Germany. Therefore, the methodology for estimating new users included both *Lamictal Tablets* and 19 generic manufacturers of lamotrigine.

Among new adult users of *Lamictal Tablets* between 1993 and 2005 based on post-marketing data, approximately 0.02% experienced confirmed SJS or TEN.[239] Among new pediatric users, approximately 0.03% experienced confirmed SJS or TEN between 1998 and 2005.

Table 20. German Registry Data: Confirmed SJS/TEN Cases in Germany During 1993-2005 Estimated New Users of Lamotrigine[239]

Year	New Peds Pts (estimate)*	New Adult Pts (estimate)*	SJS Peds (<12 years) Cases	Peds SJS/ TEN Rate (%)	SJS Adult Cases	Adult SJS/TEN Rate (%)	Total SJS Cases
1993	–	6100	0	–	5	0.08	5
1994†	–	12300	0	–	2	0.02	2
1995	–	9700	0	–	2	0.02	2
1996	–	9500	0	–	0	0.00	0
1997‡	–	10600	0	–	1	0.01	1
1998	1048	10600	1	0.10	2	0.02	3
1999	1197	12100	1	0.08	3	0.02	4
2000	1395	14100	0	0.00	4	0.03	4
2001	1592	16100	1	0.06	4	0.02	5
2002	1790	18100	1	0.06	1	0.01	2
2003	2176	22000	0	0.00	8	0.04	8
2004	2967	30000	1	0.03	3	0.01	4
2005§	4451	45000	0	0.00	4	0.01	4
Total	16615	216200	5	0.03	39	0.02	44

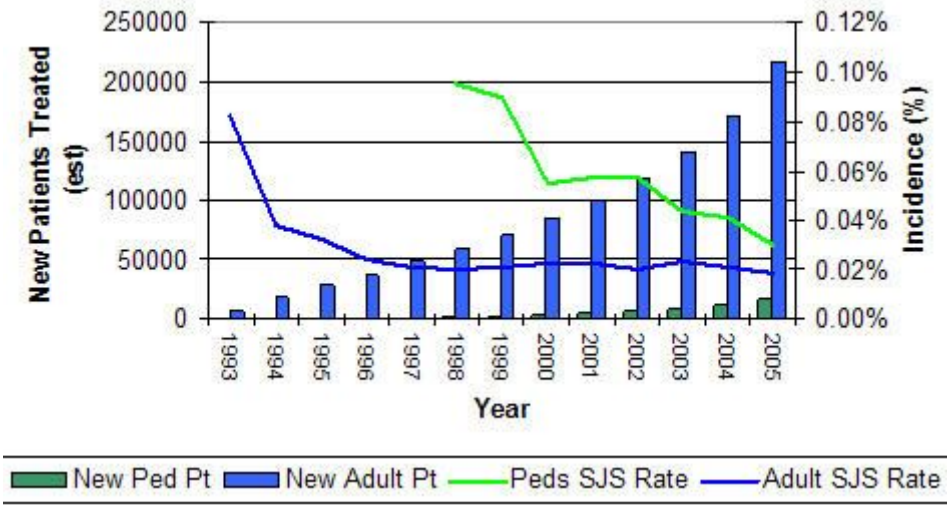
* New users were estimated based on calculations with post-marketing data

† Recommended dose of *Lamictal Tablets* in adults was changed

‡ Pediatric indication approved in Germany

§ Generic lamotrigine available in German market

Figure 15. German Rash Registry Through 2005: Cumulative Incidence of SJS/TEN Associated with Lamotrigine in Adult and Pediatric Patients[239]



The annual incidence of Stevens Johnson syndrome (SJS) and toxic epidermal necrosis (TEN) in new users of antiepileptics of *Lamictal Tablets*, phenobarbital (PB), phenytoin (PHT), and carbamazepine (CBZ) from third quarter 1998 to second quarter 2001 from the German Rash Registry was compared. [216] More than 90% of SJS and TEN cases occurred in the first 63 days of AED use. [216] The actual number of new users could be a smaller percentage of the total use of high prescription volume drugs with stable annual sales (i.e. CBZ), but a larger percentage of the total use of lower prescription volume drugs whose market share would be increasing (i.e. *Lamictal Tablets*). As a result, the number of new users was estimated from 1998 – 2001 in an additional analysis of the German Rash Registry. The risk of SJS and TEN among new users of each antiepileptic drug (AED) was estimated at 2.5/10,000 for *Lamictal Tablets*, 8.3/10,000 for PHT, 8.1/10,000 for PB, 1.4/10,000 for CBZ, and 0.4/10,000 for VPA. [216]

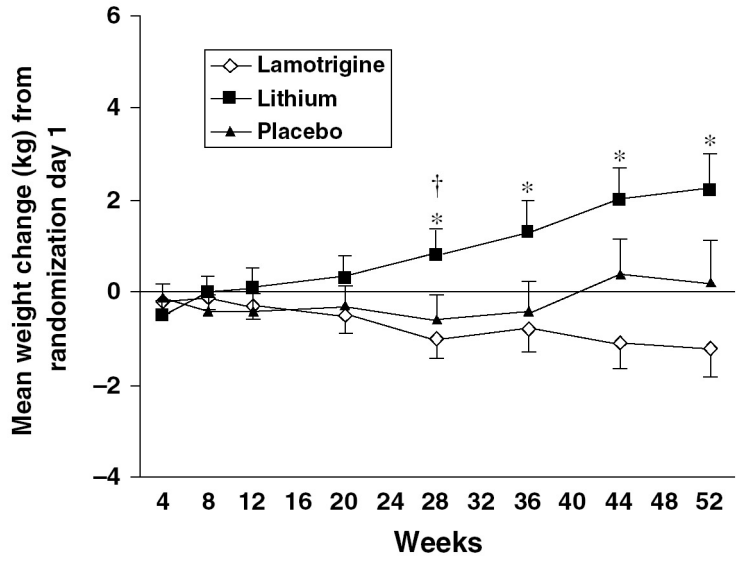
6.2 Effects on Body Weight

Patients with Bipolar

Controlled Clinical Trials

During the randomized phase of two placebo-controlled monotherapy trials of 18-months duration, adult patients with bipolar I disorder treated with *Lamictal* (100-400 mg/d fixed and flexible dosing), PBO, and lithium (0.8-1.1 mEq/L) reported weight changes of -2.6 kg (5.7 lbs), +1.2 kg (2.6 lbs), and +4.2 kg (9.2 lbs), respectively.[240] In a mixed-model repeated-measures analysis of these trials, mean changes in weight at 52 weeks of treatment were -1.2 kg (2.6 lbs), +0.2 kg (0.4 lbs), and +2.2 kg (4.8 lbs), respectively. The incidence of ≥7% weight changes and weight changes reported as adverse events were comparable between active treatments and PBO (Figure 16). Patients were initially placed on *Lamictal* with concomitant medications for up to 16 weeks prior to randomization. Patients may have gained or lost weight during this period, and this is not reflected in Figure 16. When grouping patients by pretreatment BMI (not obese = BMI < 30, obese = BMI ≥ 30) differences were evident in the obese category of patients (n = 155) at week 52: *Lamictal* –4.2 kg (9.2 lbs), lithium +6.1 kg (13.4 lbs), and PBO -0.6 kg (1.3 lbs); but not in non-obese patients (n = 399): *Lamictal* -0.5 kg (1.1 lbs), +1.1 kg (2.4 lbs), 0.7 kg (1.5 lbs)[241]

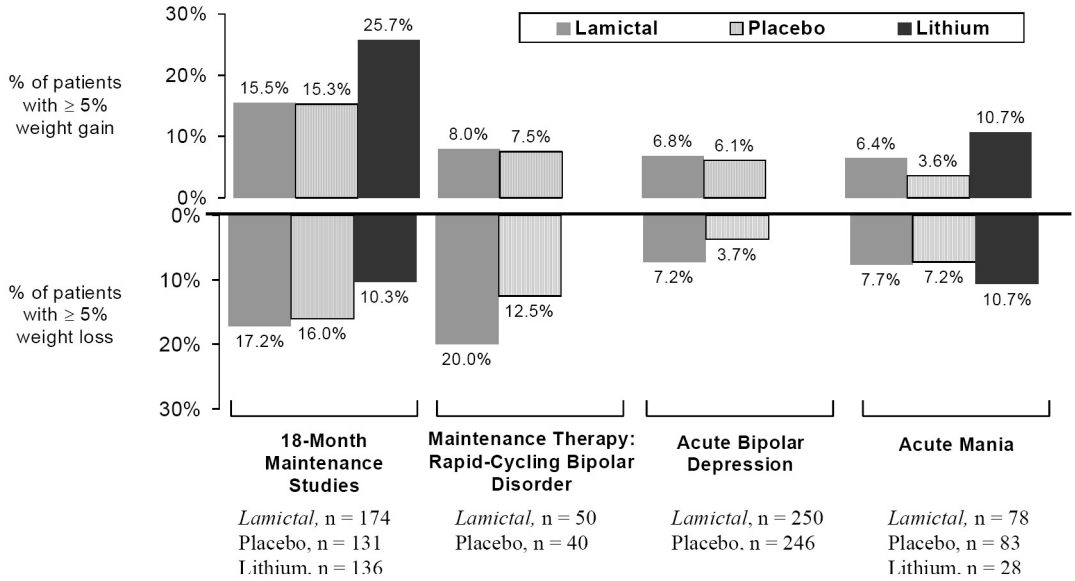
Figure 16. Mean change in weight from the first day of randomized treatment as a function of treatment week in two placebo controlled maintenance studies of *Lamictal* [240]



*p < 0.05 lithium versus lamotrigine
†p < 0.05 lithium versus placebo

The effect of *Lamictal* on body weight in patients with bipolar disorder was retrospectively analyzed from 7 double-blind, placebo-controlled trials including two 18-month maintenance trials (N = 633 for double-blind treatment) and 5 supporting trials (N = 1040; a 26-week trial in rapid-cycling bipolar disorder, 3 acute bipolar depression trials, and 1 acute mania trial).[206,207,242,243,244,245,246] The largest mean weight change over 52 weeks of treatment with *Lamictal* was approximately –2.2 lbs (-1 kg), which was not considered clinically significant. In a mixed-model repeated-measures analysis, no significant difference was observed between *Lamictal* and PBO ($P = 0.237$). In regression analyses using last-observation-carried-forward (LOCF) values, *Lamictal* did not significantly differ from PBO in mean weight change during double-blind treatment for up to 52 weeks. In the same analysis using observed-case values, a statistically significant difference in mean weight change was observed between *Lamictal* and PBO at weeks 44 and 52 ($P < 0.05$), an effect attributed to a slight weight increase in the PBO group. The incidences of ≥5% weight gain or loss (Figure 17) and of weight-related adverse events were similar between *Lamictal* and PBO.

Figure 17. Incidence of Weight Changes (5%) during the Randomized Phases of Placebo-Controlled Trials with Lamictal in Patients with Bipolar Disorder[206,207,242,243,244,245,246]



Randomized, Open-label study

In a randomized, 12-week study, outpatients (N = 1,175; aged ≥13 years, mean age 42 years) with bipolar I disorder were randomized to receive open-label treatment with *Lamictal* in addition to either blinded usual-care precautions (UCP; precautions for reducing the risk of rash, from the patient instructions in the Prescribing Information) or dermatology precautions (DP; UCP plus precautions).[195] *Lamictal* was titrated according to the Prescribing Information and adjusted for concomitant medications to a target dose of 200 mg/day. The most common (>10%) concomitant psychiatric medications were bupropion, lithium, quetiapine, valproate, citalopram, and clonazepam.

A total of 867 patients (74%) completed the study. Reasons for premature withdrawal were similar between the groups. There was no significant change in mean body weight during the study in either group. Mean weight change from baseline to week 12 was 0.0±3.82 kg in the UCP group and -0.1±3.54 in the DP group (P = NS).

Patients with Epilepsy

controlled clinical trials

Biton et al compared the effects of monotherapy with *Lamictal* and VPA on body weight in patients with epilepsy (≥12 years old) in a randomized, double-blind, parallel-group trial.[247] After completing screening and 8-week escalation phases, patients entered a 24-week maintenance phase. Of the 133 randomized patients, 65 patients received *Lamictal* (mean age, 34.5 years) and 68 received VPA (mean age, 30.1 years). Target maintenance doses were 200 mg/day (d) (range, 100-500 mg/d) for *Lamictal* and 20 mg/kg/d (range, 10-60 mg/kg/d) for VPA, although doses were adjusted based on investigators' clinical judgment.

Mean weight change was 1.3 ± 11.9 lbs for patients receiving *Lamictal* and 12.8 ± 9.3 lbs for VPA ($P \leq$ 0.002) (Figure 18). The proportion of patients with clinically significant weight gain is shown in Figure 19.

Figure 18. Mean Weight Change (Observed) Over Time in Biton et al Study[247]

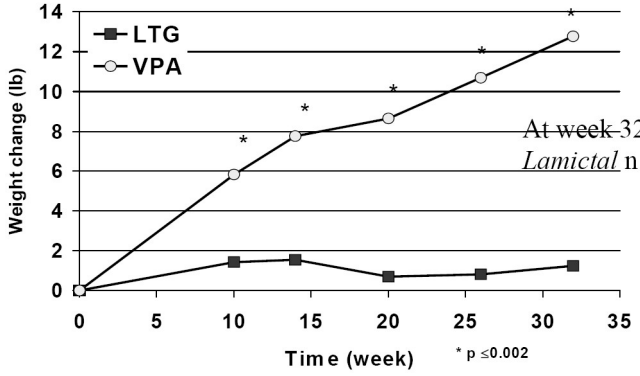
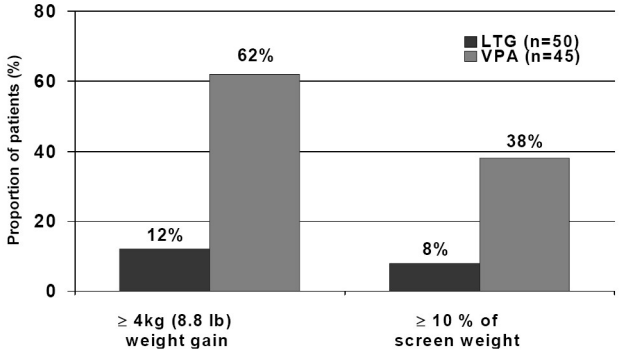


Figure 19. Proportion of Patients with Clinically Significant Weight Gain at 8 Months in Biton et al Study[247]



The mean time to withdrawal from the trial due to an adverse event was 103 ± 70 days for *Lamictal* and 79 ± 48 days for VPA. The most common drug related adverse events reported in ≥10% of patients are summarized in Table 21.[247]

Table 21. Most Common (≥10%) Drug-Related Adverse Events in Biton et al Study[247]

Adverse Event	*Lamictal* n = 65 n (%)	VPA n = 68 n (%)
Nausea	8 (12)	16 (24)
Asthenia	13 (20)	11 (16)
Somnolence	5 (8)	16 (24)
Tremor	2 (3)	19 (28)
Dizziness	7 (11)	6 (9)
Headache	9 (14)	4 (6)
Vomiting	4 (6)	9 (13)
Emotional disorder	5 (8)	7 (10)
Hair loss	2 (3)	7 (10)
Weight increase*	2 (3)	7 (10)
Appetite increase*	1 (2)	7 (10)
At least one event†	39 (60)	47 (69)
*Event may have been underreported. Only spontaneous adverse events were reported. As the objective of the trial was weight change, investigators did not probe for and report weight gain or the associated appetite increase as an adverse event unless the patient reported it. †The rate of drug-related rash was 6% (n = 4) for *Lamictal* and 4% (n = 3) for VPA.[248]		

In a subanalysis of the previous trial, Biton et al evaluated the weight effects of *Lamictal* (n = 18) and VPA (n = 20) as monotherapy in adolescent patients aged 12-20 years (mean, 16 years).[249] Mean doses as monotherapy were 261 mg/d for *Lamictal* and 1,510 mg/d for VPA. As with the overall trial population,

weight gain experienced by adolescent patients receiving VPA was significant versus *Lamictal* within 10 weeks of initiating therapy ($P < 0.05$), and did not reach a plateau during the 8-month trial. Mean body mass indexes (BMI) remained relatively stable (+0.19) in adolescents receiving *Lamictal*, but increased by +2.26 in adolescents receiving VPA.

In another subanalysis, Miller et al examined the weight effects of *Lamictal* (n = 38) versus VPA (n = 37) as monotherapy in women (mean age, 30 years).[250] Differences in weight gain between groups (*Lamictal* vs. VPA) were apparent 10 weeks after initiation of therapy (0.8 kg vs. 3.25 kg, $P = 0.0022$). Increased weight in the VPA group continued throughout the trial and did not plateau after 8 months of treatment (0.92 kg vs. 6.13 kg, $P = 0.0015$).

Kerls et al evaluated the effects of *Lamictal* as adjunctive therapy on body weight in patients with primary generalized tonic-clonic (PGTC) seizures in a randomized, placebo-controlled trial.[6,251] There were 3 trial phases: baseline; escalation, during which drug was titrated to a target dose (12 weeks for patients 2-12 years, 7 weeks for patients >12 years); maintenance, during which doses of study drug and concomitant AEDs were maintained for 12 weeks. Weight was measured at baseline and at the end of the maintenance phase. Of the 117 patients randomized, 58 received *Lamictal* (mean age, 27 years) and 59 received PBO (mean age, 25 years). Mean weight at baseline was 64 kg in patients receiving *Lamictal* and 69.1 kg in patients receiving PBO. The mean and median change in weight from baseline to the end of the maintenance treatment for patients receiving *Lamictal* (n = 35) was 0.4 kg and 0 kg, respectively and for PBO was 1.7 kg and 0.2 kg, respectively.

In a randomized placebo-controlled study, *Lamictal* (n = 132) was compared with levetiracetam (n = 136) as adjunctive therapy in patients ≥16 years of age with partial seizures.[252] There were 3 study phases: ≤2 weeks of screening, 8-week escalation, and 12-week maintenance. The primary endpoint of the study was to compare the occurrence of anger and hostility; however, weight was assessed at baseline and at the end of the maintenance phase. There was no evidence of weight gain after 20 weeks of treatment with *Lamictal*. Mean and median weight change from baseline to week 20 was -0.5 kg and 0.0 kg, respectively, in 84 patients receiving *Lamictal*.

open-label trials

In a prospective, randomized, open-label, multicenter study evaluating the development of symptoms of PCOS, women initiated either *Lamictal* or VPA as monotherapy for newly diagnosed epilepsy or as adjunctive therapy for inadequately controlled epilepsy.[253] Patients (mean age 22 years, range 13-40 years) were randomized to *Lamictal* (n = 222) or VPA (n = 225) and treated for 12 months. Eligibility criteria included regular menstrual cycles, no concurrent hormonal medications, no prior exposure to *Lamictal* or VPA, and either newly diagnosed/untreated (<2 weeks prior AED) or inadequately controlled [only 1 chronic antiepileptic drug (AED) ≥3 months] epilepsy. The median duration of exposure was 47 weeks for *Lamictal* and 48 weeks for VPA. The rates of adverse events between the two groups were similar (55% VPA vs. 56% *Lamictal*).

Mean weight gain was 2.8 kg in patients receiving VPA versus 0.2 kg in patients receiving *Lamictal* ($P < 0.001$).[254]

Isojärvi et al studied the risks associated with VPA-induced hyperinsulinemia and their reversibility after 12 months of discontinuing VPA.[255] VPA was replaced with *Lamictal* in 16 women with seizure disorders and polycystic ovaries (PCO) or hyperandrogenism. Healthy women (n = 24, mean age 29.8 years) served as controls. *Lamictal* was initiated at 25 every other day (QOD) up to a maintenance dose of 200 mg/d over five weeks while patients were receiving VPA. The dose of VPA was then tapered over three weeks. Doses of *Lamictal* could be increased up to a maximum of 500 mg/d.

Twelve of 16 women were available for follow-up evaluation. The mean duration of treatment with VPA was 9.0±5.7 years with a mean dose of 1,258 mg/d. It is important to note that in the absence of comparative data, these changes can not be attributed solely to *Lamictal*.

Refer to Table 22 for a summary of weight-related effects following discontinuation of VPA and replacement with *Lamictal*.

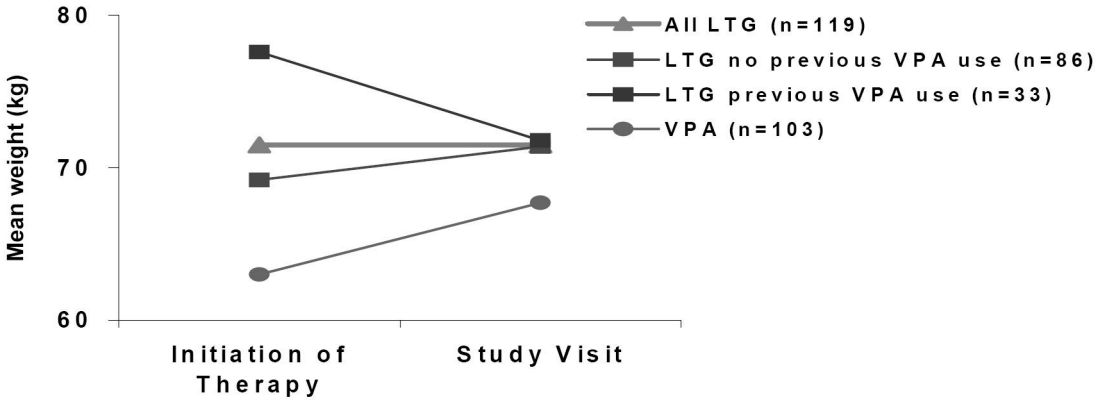
Table 22. Effects Following Discontinuation of Valproate and Replacement with *Lamictal* [255]

Clinical parameter	Effect*	Time interval
Body mass index	↓	6 mo ($P < 0.01$); 12 mo ($P < 0.001$)
Waist circumference	↓	6 mo ($P < 0.01$); 12 mo ($P < 0.001$)
Hip circumference	↓	6 mo ($P < 0.01$); 12 mo ($P < 0.001$)
Waist/hip ratio	↓	12 mo ($P < 0.01$)
*Changes based on mean ± SD values at 6 or 12-mo (month) intervals; ↓= decreased		

Morrell et al conducted a multicenter, open-label, cross-sectional, observational trial comparing endocrine and lipid measures, prevalence of menstrual disorders from patient diaries, and body weight for women with epilepsy (≤35 years) receiving long-term monotherapy with *Lamictal* (n = 119) or VPA (n = 103).[256] The trial included a screening visit, a visit on Day 1-3 of the patient's menstrual cycle, and follow-up for 3 months. The primary endpoint was comparison of total testosterone levels. Secondary endpoints included body weight measurements. Mean daily doses of *Lamictal* and VPA were 329 mg and 948 mg, respectively. The duration of pre-trial exposure to was slightly shorter for *Lamictal* than VPA (median 86.4 vs 117.4 weeks).

Mean body weight increased by 3.7 kg for VPA from the time of treatment initiation to end of trial; *Lamictal* was not associated with change in body weight (+0.2 kg). In separating weight effects by previous VPA exposure, the mean weight in patients receiving *Lamictal* with previous VPA exposure decreased (77.6 kg to 71.8 kg) compared with a neutral effect (69.2 kg to 71.4 kg) in patients without previous VPA exposure (Figure 20). Mean BMIs and waist-to-hip ratios were similar between groups.

Figure 20. Mean Weight by Treatment Group and by Previous VPA Exposure [256]



The effect of *Lamictal* on growth was evaluated in 109 children and adolescents with epilepsy.[257] Weight, height and BMI values were prospectively evaluated over 19±12 months in pediatric patients (1.6-16 years) treated with *Lamictal* as monotherapy. Patients received monotherapy with *Lamictal* at mean doses of 7.4±2.2 mg/kg (range, 3.5-14.2) for ≥6 months. Standard deviation scores at initiation of therapy versus follow-up were: height 0.07±0.42 centimeters (cm) versus 0.08±0.42 cm (P = NS); weight –0.01±0.44 kg versus -0.01±0.43 kg ($P > 0.05$); and BMI –0.24±0.47 kg/m2 versus –0.25±0.37 kg/m2 (P = NS). Body growth was considered normal regardless of age, gender, or duration of treatment.

6.3 Effects on Cognition

Controlled Studies in Patients with epilepsy

Blum et al compared the cognitive effects of *Lamictal* (n = 96) versus topiramate (TPM, n = 96) as adjunctive therapy with carbamazepine (CBZ) or phenytoin (PHY) in a multicenter, double-blind, randomized study of adults (≥18 years, mean age of 40 years) with partial seizures.[258] The study was comprised of 3 phases: baseline (≥2 weeks), 8-week dose escalation, and 8-week maintenance (without dosage changes). Target maintenance doses were 500 mg/d for *Lamictal* and 300 mg/d for TPM. The primary endpoint was change from baseline to end of maintenance on a combined analysis of 6 standard measures of cognition. These tests included following domains and measures: language (Controlled Oral

Word Association Task [COWA]), reading speed and interference (Stroop Color-Word Interference), attention/vigilance (Digit Cancellation), cognitive motor speed (Lafayette Grooved Pegboard, dominant hand), memory (Rey Auditory Verbal Learning Test [RAVLT], delayed recall), timed graphomotor coding task (Symbol–Digit Modalities test [SDMT]).

Mean daily doses during maintenance were 493.6 mg for *Lamictal* and 299.3 mg for TPM. For the primary endpoint, cognitive performance at the end of the maintenance phase was better with *Lamictal* than TPM (415.3 vs 315.1; $P < 0.001$). Significant differences favoring *Lamictal* were also demonstrated for the individual tests of COWA ($P < 0.001$), Stroop Color-Word Interference ($P = 0.038$), and SDMT ($P < 0.001$). The Performance-on-Line (POL) is a computerized test simulating driving skills which monitors scanning, divided-attention, and the effective field of view. In the subset of patients administered the POL test, simulating driving skills reflected better performance with *Lamictal* than with TPM ($P = 0.021$).[259] The change in POL hard scan scores differed significantly between groups at week 8, in favor of *Lamictal* ($P = 0.033$). Additionally, at week 16, the right and left scan were significantly different between groups in favor of *Lamictal* (right $P = 0.053$, left $P = 0.004$). The median percentage change from baseline in seizure frequency was lower with *Lamictal* than with TPM during escalation ($P = 0.028$), but not during maintenance ($P = 0.062$).[258] Other seizure efficacy rates did not significantly differ between agents. The most common adverse events (≥10%) for either group (*Lamictal* vs TPM, respectively) were headache (13% vs. 24%), dizziness (19% vs 9%), nausea (11% and 6%), and fatigue (8% vs. 13%). Rash was reported by 5 patients (5%) receiving *Lamictal* and 3 patients (3%) receiving TPM. There were no serious rashes during the study. The frequencies of cognitive adverse events and of premature withdrawals related to cognitive decline were higher with TPM than *Lamictal* (6% vs 0%; $P = 0.013$).

Pressler et al evaluated the cognitive effects of *Lamictal* as adjunctive therapy in 61 children (7-17 years, mean 11.5 years) with well-controlled or mild epilepsy receiving AED(s) in a randomized, double-blind, placebo-controlled, crossover study.[260] Patients with both partial and generalized seizure types were included. There were two 9-week treatment phases and a 5-week crossover period. A neuropsychological test battery was performed during EEG monitoring at baseline and at the end of each treatment phase. The following domains and tests were assessed: memory (Ngrams Working Memory test and FePsy Recognition Probe Test); reaction and motor speed (Binary Choice Reaction Time test); attention/vigilance (Continuous Performance test); accuracy and mental speed (FePsy Computerized Visual Searching Task), and verbal recognition (Yes-No Delayed Recognition Test). *Lamictal* was escalated to a target dose of 2 mg/kg/day (<12 years) or 150 mg/day (>12 years) in patients taking VPA and 10 mg/kg/day (<12 years) or 300 mg/day (>12 years) if not taking VPA.

Forty-eight patients completed the study. Mean lamotrigine levels were 7.6 and 8.9 mcg/mL with VPA and 3.5 and 4.6 mcg/mL without VPA. No significant difference between adjunctive therapy with *Lamictal* and placebo was found in continuous performance, binary choice reaction time, verbal and nonverbal recognition, computerized visual searching task, verbal and spatial delayed recognition, and verbal and nonverbal working memory. Seizure frequency was similar during both treatment phases. There was no significant carry-over and period effect.

Other double-blind, placebo-controlled studies evaluated cognitive measures as secondary endpoints in patients with treatment-resistant epilepsy receiving *Lamictal* as adjunctive therapy. Smith et al conducted a double-blind, cross-over, placebo-controlled, 18-week treatment phase study to evaluate adjunctive *Lamictal* 200-400 mg/day (maximum dose based on concomitant AED) in 81 adults with treatment-resistant partial epilepsy (mean age, 33.7 years; range, 15-67 years) [261] [262] No objective impairment of cognition was observed on the Stroop test, Leeds Psychomotor test, and Number Cancellation test. Banks et al conducted a double-blind, placebo-controlled, cross-over, 12-week treatment phase study of adjunctive *Lamictal* (150 mg/day with VPA and 300 mg/day with CBZ) in 12 adults with treatment-resistant partial epilepsy.[263] Neuropsychological assessments included the National Adult Reading Test (intellectual level), the Stroop Color/Word test (concentration and attention) the Trail Making Tests A + B and Digit Symbol tests (general cerebral efficiency), and the Digit Span and Rey Complex Figure test (mnestic functions). These tests were given at the beginning and conclusion of study, but no statistical tests were performed due to differing format of tests. Of the two tests considered most sensitive (Stroop Color/Word and Digit Symbol), scores reflected period changes in 7/10 patients. The recall segment of the Complex Figure Test also showed changes in six patients. Overall reduction in general

cerebral efficiency was observed during administration of *Lamictal*; however, it is unclear whether the reduction was due to *Lamictal* alone or effects of polytherapy.

Clinical Studies in Patients with bipolar disorder

Kahn et al evaluated the effects of *Lamictal* as monotherapy and as adjunctive therapy on self-reported neurocognitive measures in adult patients with bipolar I disorder in post-hoc analysis.(264) Data were derived from two large clinical studies designed to assess the efficacy of *Lamictal* as maintenance therapy in currently or recently manic (n = 349) or depressed patients (n = 966). The studies were comprised of a 2-week screening phase, an 8-16 week open-label phase, and a double-blind randomized phase lasting up to 76 weeks. During the open-label phase, *Lamictal* was titrated to a target dose of 100-200 mg/d as add-on therapy or as monotherapy, while concomitant psychotropic medications were gradually withdrawn. Eligible patients were then randomized to treatment with *Lamictal*, lithium or PBO for up to 18 months. The Medical Outcomes Study Cognitive scale (MOS-Cog) and the AB-NAS were used to measure cognitive functioning.

Based on MOS-Cog and AB-NAS scores, cognitive impairment was greater in patients with index depressive symptoms compared with patient with index manic symptoms at baseline and at the end of the open-label phase. For patients in both studies, the change in mean scores from baseline to the end of the open-label phase significantly improved for the MOS-Cog and the AB-NAS ($P < 0.0001$). Among those patients who received *Lamictal* as monotherapy, mean MOS-Cog scores also improved significantly versus baseline (+32.2 or 81%, for index depression [$P < 0.0001$] and +19.9, or 35%, for index mania [$P < 0.0001$]) and for the AB-NAS (-19.7 or -55%, $P < 0.0001$ and -7.2 or -32%, [$P = 0.0062$], respectively). Cognitive impairment was significantly inversely correlated with depressive symptom severity based on HAM-D scores ($P < 0.0001$) but not with manic symptoms based on the Mania Rating Scale.

Kaye et al evaluated changes in self-rated cognitive function with *Lamictal* as monotherapy or adjunctive therapy in post-hoc analysis of a multicenter, randomized, open-label study of 1175 outpatients (≥13 years old; mean age of 42 years) with bipolar I disorder.(265) The primary purpose of the study was to assess rash rate in patients administered dermatological precautions versus usual care.(195) *Lamictal* was titrated to a target dose of 200 mg/d (adjusted for concomitant medications) and continued for 12 weeks.(265) Cognition was measured by MOS-Cog scale via interactive voice response system at baseline and at Week 12. The intent-to-treat population consisted of 1139 patients. Mean MOS-Cog scores improved significantly from baseline in the overall group (52.1 to 61.1, $P < 0.0001$) and in subgroups of patients receiving and not receiving concomitant VPA, antidepressants, or antipsychotics. Patients receiving *Lamictal* without concomitant antipsychotics had a small but significantly greater degree of improvement than patients who were receiving concomitant antipsychotics ($P = 0.0039$). There was a statistically significant improvement in patients with index depressive ($P < 0.0001$) or manic ($P = 0.0007$) episodes. Improvements in MOS-Cog scores significantly correlated with improvement in both depressive (correlation coefficient, -0.339; $P < 0.0001$) and manic (correlation coefficient, -0.151; $P < 0.0001$) symptoms.

Pavuluri et al prospectively evaluated the effects of *Lamictal* as monotherapy on the neurocognitive profile of pediatric patients with bipolar disorder.(266) Please note that *Lamictal* is not approved for use in patients <18 years of age with bipolar disorder. They studied 65 subjects (mean age, 13 years) including 32 patients with bipolar I or II disorder, index manic, hypomanic, or mixed episodes; and 33 healthy controls matched on age, sex, race, socioeconomic status, IQ and reading ability. All subjects completed tests on attention, executive function, attention, verbal learning, working memory and emotion recognition before and after the 16-week study period. The dose of *Lamictal* was escalated for 8 weeks and maintained for 8 weeks. Rescue treatment with atypical antipsychotics was allowed only during the escalation phase. According to preliminary data, the final mean dose of *Lamictal* was 212 mg/day. There was no evidence of deterioration in any neurocognitive domain after treatment with *Lamictal*. Working memory deficits present at baseline in patients were significantly improved following treatment relative to changes in healthy controls. Facial emotion recognition improved after treatment, especially for happy child faces relative to angry and adult facial emotions. Attention domain deficits did not significantly improve. On clinical outcome measures, patients significantly improved from baseline to end of treatment on the Young Mania Rating Scale (21.74 vs 5.35, $P < 0.001$) and on the Child Depression Rating Scale (51.5 vs 24.7, $P < 0.001$).

Daban et al evaluated the cognitive measures of verbal memory, attention, and executive functions in 33 patients with bipolar I or II disorder who received *Lamictal* (n = 15) or another anticonvulsant

(carbamazepine [CBZ] or valproate [VPA]; n = 18) in an open-label study.[267] The neuropsychological battery consisted of 6 standardized measures: California Verbal Learning Test [CVLT] for verbal learning and memory, Wisconsin Card Sorting Test and verbal fluency for frontal executive functions, Stroop test for selective attention, Trail Making Test for attention and cognitive flexibility, and two tests of the Weschler Adult Intelligence Scale - digits for attention and working memory, and vocabulary subtest to estimate premorbid IQ. Patients taking *Lamictal* were generally diagnosed as having bipolar II disorder, previously experienced more depressive episodes, but a lesser number of prior hospitalizations than patients taking other anticonvulsants. Patients taking *Lamictal* had significantly better performance than other patients in the phonemic task of verbal fluency ($P = 0.008$) and trended toward statistical significance for the verbal memory task (CVLT, cued immediate recall, $P = 0.052$; CVLT, free immediate recall, $P = 0.101$). The authors stated that the moderate effect size suggested that significance may not have been reached due to the small sample size.

A naturalistic, cross-sectional study compared the cognitive effects of *Lamictal* (n = 38), valproate (n = 37), lithium (n = 30), oxcarbazepine (n = 19), topiramate (n = 19), and carbamazepine (n =16) in 159 patients (ages 18-70 years) with bipolar disorder.[268] Cognition was measured by a computerized neurocognitive screening battery, CNS Vital Signs, of 7 neuropsychological tests: verbal and visual memory, finger tapping, symbol-digit coding, the Stroop test, the shifting attention test, and the continuous performance test. When the scores of patients receiving *Lamictal* were compared with the other five mood stabilizers, significant differences were observed in favor of *Lamictal* in the neurocognition index, reaction time, cognitive flexibility, and complex attention. Rank order analysis indicated superiority for *Lamictal* (1.8) followed by oxcarbazepine (2.1), lithium (3.3), topiramate (4.3), valproate (4.5), and carbamazepine (5.0). There were significant differences for *Lamictal* versus carbamazepine ($P = 0.004$), topiramate ($P = 0.019$), valproate ($P = 0.03$), and lithium ($P = 0.043$).

6.4 Metabolic and Hormonal Effects in Women

open-label trials

In a prospective, randomized, open-label, multicenter study evaluating the development of symptoms of PCOS, women initiated either *Lamictal* or VPA as monotherapy for newly diagnosed epilepsy or as adjunctive therapy for inadequately controlled epilepsy.[253] Patients (mean age 22 years, range 13-40 years) were randomized to *Lamictal* (n = 222) or VPA (n = 225) and treated for 12 months. Eligibility criteria included regular menstrual cycles, no concurrent hormonal medications, no prior exposure to *Lamictal* or VPA, and either newly diagnosed/untreated (<2 weeks prior AED) or inadequately controlled [only 1 chronic antiepileptic drug (AED) ≥3 months] epilepsy. The median duration of exposure was 47 weeks for *Lamictal* and 48 weeks for VPA. The rates of adverse events between the two groups were similar (55% VPA vs. 56% *Lamictal*).

A greater proportion of women receiving VPA developed PCOS components compared to women receiving *Lamictal* (primary endpoint; 54% vs. 38%; $P = 0.010$).[253] In a post-hoc analysis of 363 patients ≥ 2 years past menarche, a greater proportion of patients receiving VPA developed components of PCOS (ovulatory dysfunction or hyperandrogenism) versus those receiving *Lamictal* (36% vs. 23%, respectively; $P = 0.007$). The high incidence of components of PCOS was evident in patients receiving VPA if medication was started at ≤25 years of age (44% VPA vs 23% *Lamictal*, $P = 0.002$); whereas, the incidence was similar between treatment groups if medication was started >25 years of age (24% VPA vs 22% *Lamictal*). Total testosterone levels increased significantly during the first year of treatment with VPA compared with *Lamictal* (treatment difference of 7.9 ng/dL among all patients ≥2 years past menarche, $P < 0.001$). Mean serum triglycerides increased 8.3 mg/dL in patients receiving VPA and slightly decreased by 0.1 mg/dL in patients receiving *Lamictal* ($P = 0.013$).[269] Serum total cholesterol and low density lipoprotein levels slightly decreased in both groups, but high density lipoprotein cholesterol decreased by 2.3 mg/dL for VPA and slightly increased by 0.9 mg/dL for *Lamictal* ($P < 0.001$).

Morrell et al conducted a multicenter, open-label, cross-sectional, observational trial comparing endocrine and lipid measures, prevalence of menstrual disorders from patient diaries, and body weight for women with epilepsy (≤35 years) receiving long-term monotherapy with *Lamictal* (n = 119) or VPA (n = 103).[256] The trial included a screening visit, a visit on Day 1-3 of the patient's menstrual cycle, and follow-up for 3 months. The primary endpoint was comparison of total testosterone levels. Secondary endpoints included body weight measurements. Mean daily doses of *Lamictal* and VPA were 329 mg and 948 mg,

respectively. The duration of pre-trial exposure to was slightly shorter for *Lamictal* than VPA (median 86.4 vs 117.4 weeks).

Androgen levels (mean total serum testosterone and androstenedione) were significantly higher in patients receiving VPA as compared with *Lamictal* ($P < 0.02$, primary endpoint) (Table 23). Mean cholesterol levels were significantly higher ($P < 0.05$) in patients receiving *Lamictal* compared with VPA; however, these differences were not considered clinically important. Triglyceride levels did not differ significantly between treatment groups. *Lamictal* was associated with lower blood insulin levels than VPA, although the difference was not statistically significant.

Table 23. Androgen Levels for Patients Receiving *Lamictal* and VPA [256]

Androgen Measurement	*Lamictal* (n = 119)	VPA (n = 103)	Reported Normal Reference Ranges
Mean total serum testosterone (ng/dL)	20.77	27.69*	5-63
Androstenedione (ng/dL)	2.9	3.6*	1.18-3.85

ng = nanogram; dL = deciliter; VPA = valproate

* $P < 0.02$ VPA vs *Lamictal*

Most patients reported regular menstruation at screening (*Lamictal* 87% and VPA 77%, $P = 0.07$). [256] Patients receiving VPA reported longer and more variable cycle lengths as compared with *Lamictal*. At the end of study, 90% of patients receiving *Lamictal* and 86% of patients receiving VPA completed ≥1 menstrual cycle diary record. Recorded cycle lengths (during the study) were slightly shorter for patients receiving *Lamictal* (mean 29.5 days) than for VPA (mean 31.3 days). The incidence of anovulation was similar between groups (85% with *Lamictal* versus 81% with VPA). The mean total adverse event profile (AEP) score was lower for *Lamictal* than VPA at the end of study ($P < 0.05$). [256] The individual item of shaky hands was reported as a problem significantly more for VPA than *Lamictal* (47% vs 14%, $P < 0.001$).

Timarova conducted a prospective, open-label study to assess symptoms of hyperandrogenism in women with epilepsy (15-50 years of age) receiving *Lamictal* as monotherapy.[270] Of patients receiving *Lamictal* as first-line monotherapy (n = 38), 4 (10.5%) had acne, 3 (7.9%) shortened menstrual cycle, 2 (5.3%) hair loss, and 1 (2.6%) hirsutism, oligomenorrhea, amenorrhea, or prolonged menstrual cycle at the start of therapy. Eight months later there was no significant change in the incidence of these symptoms.

Of patients switched from valproate (VPA) (n = 107), 31 (28.9%) had acne, 31 (28.9%) hair loss, 16 (14.9%) oligomenorrhea, 15 (14%) hirsutism, 13 (12.1%) shortened menstrual cycle, 11 (10.3%) prolonged menstrual cycle, and 3 (2.8%) amenorrhea at the time *Lamictal* was introduced. Eight months later, 13 (12.1%) experienced acne ($P = 0.001$), 7 (6.5%) hair loss ($P = 0.001$), 2 (1.9%) hirsutism ($P = 0.01$), 6 (5.6%) oligomenorrhea ($P = 0.01$), 6 (5.6%) shortened menstrual cycle ($P = 0.05$), 1 (0.9%) amenorrhea (nonsignificant, NS), and 8 (8.4%) prolonged menstrual cycle (NS). Of patients switched from carbamazepine (CBZ) (n = 16), the incidence of hyperandrogenism symptoms at the time *Lamictal* was introduced and 8 months later were not significantly different from the group receiving *Lamictal* as first-line monotherapy. Of patients switched from VPA and CBZ combination therapy (n = 20), 10 (50%) had acne, 9 (45%) hair loss, 8 (40%) amenorrhea, and 8 (40%) oligomenorrhea at the time *Lamictal* was introduced. Eight months later there was a significant decline in the incidence of acne, hair loss, and oligomenorrhea.

Betts et al evaluated ovarian morphology as measured by magnetic resonance imaging (MRI) in an open study of young women with primary generalized epilepsy who had only ever taken one selected AED for ≥ 1 year (VPA, n = 54 and *Lamictal* or CBZ, n = 51), and normal controls of women without epilepsy (n = 50).[271]

The prevalence of PCO (defined as >10 follicles/ovary) was significantly higher in WWE (VPA: 50%, n = 27 and *Lamictal*/CBZ: 33%, n = 17) versus controls (6%, n = 3; $P \leq 0.001$). There was no statistically significant difference in the PCO rate between the two groups of WWE. Data in women using OC suggested that they may protect WWE from having PCO, especially when taking VPA (Table 24). Women in the VPA group who experienced PCO had abnormally high testosterone and LH levels. A greater

proportion of women with PCOS were taking VPA (30%, n = 16) versus *Lamictal*/CBZ (6%, n = 3) and controls (14%, n = 7). Women receiving *Lamictal*/CBZ had a significantly lower prevalence of PCOS versus VPA ($P = 0.002$) and a statistically similar rate to controls.

Table 24. Prevalence of PCO and PCOS in WWE and Controls Based on Oral Contraceptive Use [271]

Treatment Group	OC Use*	N*	Polycystic Ovaries		Polycystic Ovarian Syndrome	
			Non-PCOS % (N)	PCOS Present % (N)	Non-PCOS % (N)	PCOS Present % (N)
Valproate						
	Yes	15	80 (12)	20 (3)	80 (12)	20 (3) ‡
	No	39	41 (16)	59 (23) †	67 (26)	33 (13)
Lamictal/Carbamazepine						
	Yes	14	86 (12)	14 (2)	93 (13)	7 (1) ‡
	No	37	59 (22)	41 (15) †	95 (35)	5 (2)
Normal Controls						
	Yes	23	91 (21)	9 (2)	96 (22)	4 (1) ‡
	No	27	96 (26)	4 (1) †	77 (21)	23 (6)

N=number of patients, OC=oral contraceptive, PCO=polycystic ovaries, PCOS=polycystic ovarian syndrome

*Between groups: no significant difference between the 3 groups taking OC

†Within groups: PCO rate with OC use vs no OC use was $P = 0.001$ for valproate and no significant difference for *Lamictal*/CBZ or controls

‡Between groups: no significant differences in PCOS rate when taking OC

As part of a larger observational study evaluating reproductive health in WWE, Morrell et al assessed whether WWE are more likely to have anovulatory cycles and the relative association of epilepsy syndrome and AEDs to ovulatory dysfunction. [272,273] Subjects (18-40 years, mean age 31 years), not receiving hormones or diagnosed with a condition that could influence study parameters, included 23 controls (women without epilepsy), 59 women with localization-related epilepsy (LRE), and 35 women with idiopathic (primary) generalized epilepsy (IGE). Patients received monotherapy for ≥ 6 months with either an enzyme-inducing antiepileptic drug (EIAED; CBZ n = 21, PHY n = 15, and phenobarbital n = 13), an inhibiting AED (VPA n = 21), or an AED not altering CYP enzymes (*Lamictal* n = 16 and gabapentin [GBP] n = 8). Subjects were followed for three menstrual cycles or three months with transvaginal ovarian ultrasounds, home ovulation kits, endocrine and metabolic variables, basal body temperatures, and LH samples.

Anovulatory cycles occurred in 10.9% of cycles in controls, 14.3% with LRE, and 27.1% with IGE. [272] Of women receiving VPA currently or within the preceding three years, 38.1% had ≥1 anovulatory cycle in contrast with 10.7% of women not receiving VPA within three years. There were sufficient numbers of women in each syndrome group receiving PHY (10 LRE, 5 IGE) and *Lamictal* (7 LRE, 7 IGE) to analyze the effect of syndromic category and AED on endocrine variables. In women receiving PHY, estrone was significantly lower (20.0 vs 35.1 pg/mL; $P = 0.0002$), DHEAS was significantly lower (330 vs 1,267 ng/mL; $P = 0.002$), and SHBG was significantly higher (163 vs. 96 nmol/L; $P = 0.009$) compared with women receiving *Lamictal*. In an analysis of women with LRE versus controls (n = 20), estrone was lower with CBZ (20.7 pg/mL) and higher with *Lamictal* (37.5) versus controls (26.9; $P = 0.006$).

Stephen et al studied the hormone profiles of young women (mean age 33 years, range 17-50) and men with epilepsy taking *Lamictal* (n = 36) or VPA (n = 40) as monotherapy. [274] Of these, 23 women were receiving VPA and 21 were receiving *Lamictal* for ≥ 2 years. Daily doses of VPA and *Lamictal* ranged from 400-2500 mg (mean, 1929 mg) and 50-600 mg (mean, 276 mg), respectively. None of the women were receiving hormonal replacement or contraceptives. Baseline biochemical parameters, age, and seizure types were similar between groups. In women taking VPA as compared with *Lamictal*, there were significantly higher values of testosterone ($P = 0.02$), free androgen index ($P = 0.03$), triglycerides ($P = 0.02$) and insulin levels. Obese patients of both sexes ($P = 0.01$) had higher insulin concentrations. Four obese VPA-treated women were hyperinsulinaemic ($P < 0.05$); three with abnormal menstrual cycles and one with increased testosterone.

Khatami evaluated the natural course and significance of PCO as a possible risk factor for the development of PCOS in WWE receiving CBZ, VPA, or *Lamictal*. [275] In this observational study, 26 women (16-43 years) had serial endocrine and metabolic assessments and transvaginal ultrasonography and follow-up at 2, 6 and 12 months after baseline examination. The prevalence of PCO on ultrasonography without anovulatory cycles and clinical signs of hyperandrogenism was 46% (12/26) and PCOS was diagnosed in 19% (5/26). Prevalence of PCOS by AED was 26% (4/15) for VPA, 20% (1/5) for CBZ, and 0% (0/7) for *Lamictal*. Compared to women with normal ovaries, those with PCO had nonsignificantly higher LH to FSH ratios and free testosterone concentrations. No differences were found in BMI, hip-waist ratio, or metabolic parameters. At follow-up through 6 months, morphologic structure of PCO on ultrasonography disappeared in two women (one receiving VPA and one CBZ). During follow-up, none of the PCO-negative women developed PCO and none of the women with PCO developed clinical or laboratory hyperandrogenism.

Isojärvi et al studied the risks associated with VPA-induced hyperinsulinemia and their reversibility after 12 months of discontinuing VPA.[255] VPA was replaced with *Lamictal* in 16 women with seizure disorders and polycystic ovaries (PCO) or hyperandrogenism. Healthy women (n = 24, mean age 29.8 years) served as controls. *Lamictal* was initiated at 25 every other day (QOD) up to a maintenance dose of 200 mg/d over five weeks while patients were receiving VPA. The dose of VPA was then tapered over three weeks. Doses of *Lamictal* could be increased up to a maximum of 500 mg/d.

Twelve of 16 women were available for follow-up evaluation. The mean duration of treatment with VPA was 9.0±5.7 years with a mean dose of 1,258 mg/d. It is important to note that in the absence of comparative data, these changes can not be attributed solely to *Lamictal*.

Refer to Table 25 for a summary of effects following discontinuation of VPA and replacement with *Lamictal*.

Table 25. Effects Following Discontinuation of Valproate and Replacement with *Lamictal* [255]

Clinical parameter	Effect*	Time interval
Fasting serum insulin	↓	2 mo, 12 mo ($P < 0.01$); 6 mo ($P < 0.05$)
Serum testosterone levels	↓	2, 6, 12 mo ($P < 0.001$)
Total serum cholesterol	↔	-
Serum HDL-cholesterol	↑	-
Serum HDL-cholesterol/total cholesterol ratio	↑	6, 12 mo ($P < 0.001$)
Serum triglycerides	↓	2, 6, 12 mo ($P < 0.001$)
*Changes based on mean ± SD values at 2, 6, or 12-mo (month) intervals ↓ decreased, ↑ increased, ↔ no change, HDL = high density lipoprotein		

There were a total of 20 PCO in the 12 women while receiving VPA.[255] The total number of PCO decreased to 11 at 12 months after discontinuation of VPA ($P < 0.01$). Although the number of ovarian follicles and mean volume of the ovaries decreased after discontinuation of VPA, this was not statistically significant after one year. Of the 12 women studied, seven had menstrual disturbances during VPA use, but menstrual cycles normalized in five of the women during the first year of therapy with *Lamictal* ($P < 0.05$).

Kim et al prospectively investigated potential hormonal and metabolic abnormalities in Korean women (range 18-45 years) with epilepsy receiving *Lamictal* (n = 12), carbamazepine (CBZ, n = 19), valproic acid (VPA, n = 12), or topiramate (TPM, n = 11) as monotherapy for > 6 months.[276] Patients recorded their menstrual and seizure information in diaries for > 3 months (or > 3 menstrual cycles). There were no differences in hormonal and metabolic indices or rates of menstrual irregularity between patients diagnosed with primary generalized epilepsy (n = 18) and localization-related epilepsy (n = 36). Menstrual irregularity was twice as frequent in patients receiving VPA than patients receiving *Lamictal*, CBZ or TPM *(P* = NS). Menstrual cycles were irregularly prolonged in VPA-treated patients compared with *Lamictal*, CBZ, and TPM ($P = 0.015$). Body mass index and rates of metabolic syndrome were higher in patients

receiving VPA than those receiving *Lamictal*, CBZ, and TPM ($P < 0.05$). High density lipoprotein (HDL) cholesterol was lower in VPA-treated patients compared with *Lamictal*, CBZ, and TPM ($P = 0.002$). No significant differences were observed in weight, waist/hip ratio, triglycerides, total cholesterol, low density lipoprotein (LDL) cholesterol, fasting-insulin, leptin, HOMA-index, or insulin resistance.

6.5 Effects on Bone Health

CLINICAL INFORMATION

Adults

Pack et al evaluated bone turnover and bone mass in 93 outpatient women with epilepsy (WWE) aged 18 to 40 years receiving ≥ 6 months of AED monotherapy in a prospective, cross-sectional study. [277] Patients were receiving carbamazepine (CBZ, n = 37), *Lamictal* (n = 19), phenytoin (PHY, n = 19), or valproate (VPA, n = 18). The average duration of treatment with *Lamictal* was significantly less than for other agents (21 months vs. 66 months to 97 months, $P = 0.001$). Other baseline characteristics were similar. Adverse event information was not reported. There were no significant differences between groups were found for BMD Z-scores, osteocalcin, crosslinked n-telopeptides of type 1 collagen (NTx), parathyroid hormone (PTH), or the proportion of patients who had vitamin D levels in the insufficient range. Vitamin D levels for each group were within normal levels, although no patient receiving *Lamictal* had vitamin D levels in the insufficient range. IGF-I (growth factor that enhances osteoblastic differentiation and increases bone formation) levels were significantly reduced in patients receiving PHY compared to *Lamictal* ($P = 0.017$). There were no significant differences in IGFBP-3 (binding protein shown to modulate IGF-mediated effects) levels among the groups. Patients receiving PHY had significantly greater bone specific alkaline phosphatase (BSAP) concentrations than those receiving *Lamictal*, CBZ, and VPA ($P = 0.007$). A significant reduction in calcium levels was found in patients receiving CBZ, PHY, and VPA compared to those receiving *Lamictal* ($P = 0.008$). No correlation between calcium concentrations and duration of treatment with *Lamictal* was detected.

Additionally, Pack et al evaluated BMD changes after one year of AED treatment in adult (mean age, 32 years) women with epilepsy.[278] Patients received CBZ (n = 41), *Lamictal* (n = 23), PHY (n = 15), or VPA (n = 14). Baseline characteristics were similar between groups with the exception of age (patients taking *Lamictal* or VPA were significantly younger, $P = 0.03$) and total duration of exposure to AEDs (patients taking CBZ or PHY had significantly longer exposure, $P = 0.04$). Baseline Z-scores (range: -0.51 – 0.22) did not differ among groups. BMD was stable at the lumbar spine and total hip in all groups after one year of treatment. There was significant bone loss in the PHY group at the femoral neck when compared to CBZ ($P < 0.03$) and VPA ($P < 0.02$), but not *Lamictal*. There was a trend ($P = 0.09$) toward an association between longer AED use and lower 1-year rates of bone loss at the total hip, regardless of specific AED. Patients taking PHY had significantly lower urine NTx at 1 year versus baseline ($P < 0.05$). Serum calcium was significantly higher in patients taking *Lamictal* compared to the CBZ, PHY, and VPA groups ($P = 0.04$). Only VPA demonstrated a significant association between vitamin D and serum PTH, BSAP, and urine NTx ($P < 0.04$ all).

Spasic et al compared serum calcium levels in 130 men with epilepsy receiving AED monotherapy.[279] Patients received *Lamictal* (n = 30), CBZ (n = 40), VPA (n = 25), phenobarbital (PB, n = 15), PHY (n = 12), or topiramate (TPM, n = 8) for >6 months. According to preliminary data, all calcium serum levels were within the normal range. Calcium levels were reduced in men receiving CBZ, phenobarbital (PB), PHY, and VPA compared to *Lamictal* and TPM, although results did not reach statistical significance.

Stephen et al measured BMD in 78 patients (47 post-menopausal women and 31 men; age range of 47-76 years, median age 58 years) with epilepsy (26 idiopathic, 52 partial) in a case-control study. [280] Each had only received treatment with either enzyme-inducing AEDs (EIAEDs, CBZ, PHY, and PB) (n = 52) or non-EIAEDs (*Lamictal*, VPA, vigabatrin, TPM, or gabapentin) (n = 26). Length of AED treatment ranged from 5-36 years (mean 23 years for EIAEDs and 10 years for non-EIAEDs). Serum PTH, 25-hydroxyvitamin D, osteocalcin, and urine deoxypyridinoline were measured as biochemical markers of bone metabolism.

Forty-eight (26 women and 22 men) patients (61%) reported a history of fractures, but only three (6%) of these were seizure-related. Men had significantly lower BMD than controls at both lumbar spine and femoral neck, while women had reduced BMD only at the femoral neck. No significant differences in

BMD were detected between patients receiving EIAEDs and non-EIAEDs. Both groups had lower BMD at the femoral neck and lumbar spine than normal age and sex-matched controls. However, patients receiving EIAEDs had lower vitamin D concentrations than controls. None of the patients receiving non-EIAEDs had lower vitamin D concentrations.

Kim et al prospectively investigated alterations in BMD and markers of bone metabolism in drug-naïve Korean patients (mean age 26 years, range 18-50 years) with newly diagnosed epilepsy receiving *Lamictal* (n = 8), CBZ (n = 10), or VPA (n = 15) as initial monotherapy.[281] Patients were excluded if they had a history of taking an AED or any medication that may affect bone metabolism, had a medical disorder likely to affect bone health, had impaired motor function, or was pregnant, breastfeeding, or menopausal. BMD at right calcaneus and various markers for bone metabolism were measured by DEXA before and after 6 months of AED monotherapy treatment.

Twenty men and 13 women completed the study. Daily intakes of calcium and vitamin D and amount of daily exercise did not differ among the AED groups. After 6 months of treatment, BMD Z-scores decreased significantly only in patients receiving CBZ ($P = 0.043$). Only treatment with CBZ significantly decreased vitamin D values ($P = 0.018$). Osteocalcin, a marker of bone formation, increased twofold with *Lamictal* ($P = 0.012$) and VPA ($P = 0.002$). Parathyroid hormone levels markedly increased in all 3 AED groups: $P = 0.043$ (*Lamictal*), $P = 0.004$ (CBZ), $P = 0.001$ (VPA). No significant differences were observed in total calcium, ionized calcium, phosphorus, alkaline phosphatase, or Pyrilinks between the three AED groups.

Vestergaard et al performed a population-based case-control study to assess fracture risk associated with AEDs over five years. [282] After adjustment for confounders (prior fracture, history of corticosteroid use, comorbidity, social variables, diagnosis of epilepsy), fracture risk associated with *Lamictal* was not statistically significant. However, *Lamictal* was associated with an increased fracture risk in the spine. No dose-response relationship was demonstrated for *Lamictal*.

Children and Adolescents

Sheth et al measured total z-score bone mineral density in 53 outpatient children with epilepsy and 36 control subjects in a cross-sectional study.[283] The children with epilepsy included 13 receiving *Lamictal* as monotherapy and not previously exposed to other medications and 40 exposed to polytherapy. All patients were ambulatory and had similar physical activity and calcium intake. Groups were comparable with regard to race (all Caucasian) and age.

Patients received *Lamictal* for a duration of 4 ± 3.3 years (range, 1.1-13 years). Examination of height and weight percentiles revealed no significance differences between patients with epilepsy and control subjects. The z-scores of bone mineral density in patients receiving *Lamictal* were similar to control subjects (0.49 ± 0.7 versus 0.52 ± 0.76) and higher than in patients receiving polytherapy for 1-5 years and ≥6 years (0.14 ± 0.8 and 0.24 ± 1.15). Increasing duration of epilepsy was associated with a statistical trend ($r = +0.17$, $P = 0.16$) toward increased bone density in patients receiving *Lamictal*; thereby suggesting normal bone mass accrual.

Guo et al evaluated the long-term effects of >2 years treatment with *Lamictal* and/or VPA on growth and/or bone metabolism in charts of 27 boys and 26 girls (mean age of 9 years, range 3-17 years) with epilepsy. [284] Children receiving other medications known to affect bone metabolism, having other diseases that might alter growth or bone health, or having a family history of osteoporosis were excluded. Measurements included growth, nutrient intakes, physical activity, BMD, and blood biochemical markers of mineralization and bone metabolism.

Among the overall study participants, 23 (43.4%) had a body height below the tenth percentile. Compared with reference values, levels of plasma intact PTH (sensitive biochemical marker of bone formation) were in the lower limit while plasma 25-hydroxyvitamin and plasma 1,25-dihydroxy vitamin D were within normal ranges for all subjects. Z-score for total body BMD was correlated with daily activity score ($r = 0.43$, $P = 0.008$). When dividing patients into three treatment groups of *Lamictal* (n = 16), VPA (n = 28), and combined therapy with *Lamictal* and VPA (n = 9), lower body height percentile and plasma osteocalcin ($P < 0.05$) were found in the combined therapy group as compared with monotherapy groups. However, the mean physical activity score was 25% and 32% lower in the combined therapy group compared with *Lamictal* or VPA alone. Dosing and adverse events were not provided.

6.6 Effects on Behavior and Mood

In Adults with Epilepsy

product label information

Behavioral and mood-related adverse events reported in placebo-controlled adjunctive trials of *Lamictal* for partial seizures in adults (≥16 years) at a rate of ≥2% were similar to PBO and included: depression (4% with *Lamictal* vs 3% with PBO), anxiety (4% vs 3%), and irritability (3% vs 2%).(90)

A randomized, double-blind, multicenter trial compared behavioral changes associated with *Lamictal* (n = 132) or levetiracetam (LEV, n = 136) as adjunctive therapy in adult patients (≥16 years) with partial seizures.(285) Patients experiencing ≥2 simple or complex partial seizures with or without secondary generalization during the 6 months prior to study entry and were receiving a stable dose of carbamazepine or phenytoin with or without one other antiepileptic drug were included in the trial. Over the 8-week escalation phase, patients were titrated from an initial dose of *Lamictal* 50 mg/day to a target maintenance dose of 400 mg/day or from an initial dose of LEV 500 mg/day to a target maintenance dose of 2000 mg/day. Adjustments to the target dose were allowed during the 12-week maintenance phase to maintain seizure control or reduce adverse events. The mean change in the Anger-Hostility subscale score of the Profile of Mood States (POMS) between baseline and end of maintenance phase (primary endpoint) was -2 (±8.2) versus -0.3 (±8.4) in patients receiving *Lamictal* and LEV, respectively ($P = 0.024$). The median percent decrease in seizure frequency from baseline to end of maintenance phase was 60% with *Lamictal* and 65% with LEV ($P = 0.501$). The most common adverse events (≥10%) for *Lamictal* or LEV, respectively, were headache (32%; 25%), dizziness (13%; 15%), nausea (11%; 10%), fatigue (8%; 11%), somnolence (5%; 12%), nasopharyngitis (6%; 10%), and irritability (6%; 10%). Rash was reported in 6% of patients receiving *Lamictal* and 7% receiving LEV; no cases were serious. Eleven percent of patients receiving *Lamictal* withdrew due to adverse events versus 18% receiving LEV.

Edwards et al discussed secondary measures of mood assessments from a randomized, double-blind, parallel-group trial in newly diagnosed patients (≥12 years old) with epilepsy designed to compare the effects of monotherapy with *Lamictal* and monotherapy with valproate (VPA) on body weight. (286) The trial was not powered to detect differences in mood scores. After completing a 2-week screening phase and an 8-week escalation phase, patients entered a 24-week maintenance phase. After randomization, patients completed 3 mood assessment questionnaires including the Beck Depression Inventory (BDI), the Cornell Dysthymia Rating Scale (CDRS)-Self Report and the Profile of Mood States (POMS) at week 10 and week 32, corresponding to the second and last week of the maintenance phase, respectively. Mean scores on the 3 mood scales at screening were similar between groups. Mean scores of 10.4 – 11.9 on the BDI reflected mild depressive symptoms. Of the 133 randomized patients, 65 patients received *Lamictal* (mean age, 34.5 years) and 68 received VPA (mean age, 30.1 years); 112 patients entered the maintenance phase, and 84 patients completed the trial. Target maintenance doses were 200 mg/d (range 100-500 mg/d) for *Lamictal* and 20 mg/kg/day (d, range 10-60 mg/kg/d) for VPA, although doses were adjusted based on investigators' clinical judgement. The mean doses of and VPA during the maintenance phase were 254 mg/d and 1822 mg/d, respectively.

Mean BDI scores and CDRS scores for patients treated with *Lamictal*, but not with VPA, improved at week 10 of the maintenance phase. For BDI scores, improvement in patients treated with *Lamictal* was enhanced at week 32 and was approximately four times higher than in patients treated with VPA. For CDRS scores, the improvement in patients treated with *Lamictal* was enhanced at week 32 and was approximately seven times higher than in VPA-treated patients. POMS scores for patients treated with *Lamictal*, but not with VPA, improved compared with baseline at weeks 10 and 32. Improvements with *Lamictal* were especially marked for total mood disturbance, which improved by nearly 14 points by week 32, and for depression-dejection, which improved by nearly 4 points by week 32. At the end of 8 months, significantly more patients receiving *Lamictal* compared with VPA experienced QOL improvements on the Health Perceptions (42% vs 15%), Energy/Fatigue (47% vs 28%), and Social Isolation (35% vs 16%) subscales of the Quality of Life in Epilepsy (QOLIE)-89 questionnaire ($P < 0.05$). (287)

The most common drug-related adverse events for *Lamictal* and VPA respectively were nausea (12%; 24%), asthenia (20%; 16%), somnolence (8%; 24%), and tremor (3%; 28%).

A subanalysis of a multicenter, randomized, double-blind, placebo-controlled trial of *Lamictal* as adjunctive therapy in 117 patients with primarily generalized tonic clonic (PGTC) seizures evaluated effects on depressive symptoms in patients ≥16 years of age (*Lamictal*: n = 32, mean age 35 years; placebo (PBO): n = 38, mean age 33 years).[288] The analysis involved patients who completed 3 mood questionnaires - Beck Depression Inventory, second edition (BDI-II), Profile of Mood States (POMS) and Cornell Dysthymia Rating Scale (CDRS) - at screening and at the end of maintenance treatment. Mean maintenance *Lamictal* doses were 395 mg/day in patients taking concomitant enzyme-inducing antiepileptics (AEDs), 187 mg/day in patients taking valproate, and 233 mg/day in patients taking other AEDs, such as gabapentin, oxcarbazepine, and topiramate. Scores showed mild depressive symptoms at baseline across both groups. After maintenance treatment, patients receiving *Lamictal* experienced significant improvement in BDI-II and POMS scores versus PBO (-8.9 vs -1.7 [$P = 0.01$] and -32 vs -6.5 [$P = 0.03$], respectively), but not in CDRS scores (-7.3 vs -4.1 [$P = 0.5$]). The most common drug-related adverse events for *Lamictal* and PBO respectively were dizziness (6% vs 3%), somnolence (6% vs 0%), diplopia (6% vs 0%), nausea (3% vs 5%), and headache (0% vs 5%).

Open-Label Trials

Cramer et al evaluated changes in mood and quality of life (QOL) associated with *Lamictal*, as adjunctive therapy and monotherapy as part of a 16-week open-label trial of outpatients (N = 196; mean age, 43 years) with epilepsy. [289] Patients taking a single enzyme-inducing AED (e.g., carbamazepine, phenytoin, phenobarbital, and primidone) were eligible to convert to monotherapy with *Lamictal* for an additional 12 weeks. Of the 196 patients, 155 completed the adjunctive phase and 51 completed the monotherapy phase. Mean doses of *Lamictal* during the adjunctive and monotherapy phases were 278 mg/d and 386 mg/d, respectively. At baseline, patients reported mood problems that were approximately two times as high as estimates from a healthy control population in all POMS scales and four times higher in total scores. Among all patients completing the adjunctive phase, all scale scores were improved from baseline (all $P < 0.0001$). All POMS scores were statistically improved ($P < 0.003$) in patients completing both the adjunctive and monotherapy phases. Total scores improved 28 ± 38.7 at the end of the adjunctive phase and 29.9 ± 9.2 at the end of the monotherapy phase. At the end of the monotherapy phase, POMS and Quality of Life in Epilepsy (QOLIE-31) scores remained significantly better than baseline (all $P \leq 0.003$), but not from the end of the adjunctive phase. Seizure reduction was not significantly associated with changes in POMS scores.

A multicenter, open-label, 36-week trial evaluated the effect of *Lamictal* added to stable regimens of a single AED in reducing depressive symptoms in adults patients with epilepsy (N = 158; mean age, 39 years).[290] Mood changes were measured by self-report scores on the Beck Depression Inventory, second edition (BDI-II), Center for Epidemiological Studies Depression Scale (CES-D), the Neurological Disorders Depression Inventory in Epilepsy (NDDI-E) and POMS. Patients had low to moderate depressive symptoms (CES-D score ≥12), but not medications for or diagnosis of Major Depressive Disorder (by MINI). Trial phases included a screen (≤2 weeks); escalation (7 weeks), maintenance (12 weeks), and withdrawal (5 weeks) during adjunctive therapy; and monotherapy period (12 weeks). The most common concomitant AEDs were phenytoin (31%), CBZ (19%), and VPA (15%). In both the intent-to-treat population and those who entered the monotherapy phase, mean depression scores significantly ($P < 0.0001$) decreased from baseline to the end of the adjunctive phase (n = 96) on all scales. Significant improvement on depression scores continued on all scales at the end of the monotherapy phase (n=66; $P < 0.0001$ versus baseline). The most common (≥ 5%) adverse events were dizziness (13%), headache (11%), nausea (9%), fatigue (7%), blurred vision (6%), and rash (5%). In a subanalysis of 40 older patients (≥ 50 years old) who received *Lamictal*, mean depression scores significantly decreased from baseline to the end of the adjunctive phase for the CES-D and POMS ($P < 0.01$), and significantly decreased from baseline to the end of the monotherapy phase for all scales ($P < 0.01$).[291] The types and incidences of adverse events in older adults were similar to those in the overall study population.

In an open, randomized, parallel group, multicenter add-on trial, Crawford et al compared the effects of *Lamictal* and gabapentin (GBP) on efficacy, behavior, and mood (N = 109) in adult (mean age 36 years; range 15 - 67 years) patients with learning disabilities and resistant epilepsy (taking 1 - 3 AEDs without satisfactory seizure control). [292] Study medications were increased over 14 weeks at the discretion of the investigators, to a maximum dose of 400 mg/day for *Lamictal* (200 mg/day with concomitant valproate) and 3600 mg/day for GBP. Mean doses were 207 mg/d for *Lamictal* and 1749 mg/d for GBP. Similar

percentages of patients experienced a ≥50% seizure reduction after the addition of *Lamictal* or GBP (49% vs 50%, *P* = NS). Seizure-free rates were 11.4% for *Lamictal* and 7.7% for GBP. Both treatment groups experienced overall behavioral improvement after the addition or *Lamictal* or GBP; neither agent appeared to exacerbate challenging behaviors observed in this patient population. Specifically, the carer-rated visual analogue scales detected statistically significant improvements ($P < 0.05$) for *Lamictal* in seizure severity and for GBP in seizure severity, attention, general health, and sleeping pattern. The safety profile reported was similar to previous trials.

Thirteen patients (21-55 years) with uncontrolled partial seizures and concomitant symptoms of depression (that did not meet DSM-IV criteria for major depressive disorder) were evaluated to determine the effect of adding open-label *Lamictal* on depressive symptomatology. [293] The Montgomery and Asberg Depression Rating Scales (MADRS), the depression scale of the Minnesota Multiphasic Personality Inventory (MMPI), and the Spielberger's State-Trait Anxiety Inventory (STAI) were administered at 5 weeks and 3 months. *Lamictal* was initiated at 25 mg twice daily and titrated over 9 weeks to 250 mg twice daily as tolerated (with dose reduction in patients taking valproate). Twelve patients completed the study. The mean dose of *Lamictal* was 143.2 mg/day at 5 weeks and 392.5 mg at 3 months. Compared to baseline, overall MADRS scores significantly decreased at 5 weeks ($P = 0.002$) and 3 months ($P = 0.010$). Significant reductions from baseline occurred on the depression scale of the MMPI at 3 months ($P = 0.033$), but not at 5 weeks. Both State and Trait mean anxiety scores significantly improved from baseline at 5 weeks (P=0.014 and $P = 0.026$, respectively). At 3 months, only the mean Trait anxiety score maintained a significant reduction compared to baseline ($P = 0.025$), although State anxiety scores decreased from pretreatment baseline in 7 of 9 patients who took the STAI. Side effects were transient or responded to dosage reduction.

In Children and Adolescents with Epilepsy

CLINICAL Information

Controlled Clinical Trials

In a randomized, double-blind, placebo-controlled adjunctive trial of 169 patients (age range, 3-25 years) with LGS, neurologic examinations showed significant improvements for patients treated with *Lamictal* compared with patients receiving placebo (PBO) in behavior (30% vs 14%), speech (11% vs 2%), nonverbal communication (11% vs 8%), and gross coordination (5% vs 4%).[205] [7]

Pressler et al assessed the effect of suppression of interictal EEG discharges on behavior in 61 children and adolescents (7-17 years) with behavioral disturbances and well-controlled or mild epilepsy in a double-blind, placebo-controlled, crossover trial. [294] Ambulatory electroencephalograms (EEGs) and behavioral scales were performed at baseline and at end of treatment phases. *Lamictal* or PBO was added to the current antiepileptic drug (AED) regimen, each for 13 weeks. The dose of *Lamictal* differed based on ≤ or >12 years of age and concomitant valproate (VPA). Patients who showed a significant reduction in either frequency or duration of discharges during treatment with *Lamictal* experienced significant improvement in global rating of behavior ($P < 0.05$). This effect was mainly seen in patients with partial seizures ($P < 0.005$). Results were not affected by the order of randomization, change in seizure frequency, or Intelligence Quotient (IQ).

Uvebrant and Bauziene conducted an open-label study of *Lamictal* as monotheray or adjunctively in 50 patients (mean age, 8 years; range, 1 – 20 years) with intractable epilepsy (at least two seizures a month despite treatment with first-line antiepileptic drugs (AEDs) as monotherapy and in combination).[295] Forty patients (80%) had mental retardation. Mean duration of treatment was 14 months (range, 4 – 35 months). *Lamictal* was iniated at 0.3 – 2.2 mg/kg/d based on concomitant AEDs. The mean dose of *Lamictal* was 4.5 mg/kg/day. Six patients received *Lamictal* as monotherapy. Of 45 patients, 5 (11%) became seizure free, 16 (36%) experienced > 30% reduction in seizures, 24 (53%) experienced no change, and 3 (6%) experienced an increase in seizures. Similar response rates were seen patients with partial or generalized seizures. Based on the reports of the parents of 24 children, improvements were noted in contact, attention, alertness, and irritability. Negative behavior effects included aggressiveness (n = 1), hyperactivity (n = 1), psychosis relapse (n = 1), and hallucinations (n = 1). Eight of thirteen patients experienced a decrease in autistic symptoms, and two of three patients experienced improvement in attention deficit hyperactivity disorder. The most common adverse events were sleep disturbance (14%), rash (10%), and hair loss (4%).

Franz et al presented experience with *Lamictal* in 57 patients (5-35 years) with tuberous sclerosis in which behavior and alertness subjectively improved in 18 (32%) patients, remained unchanged in 38 (67%), and worsened in 1 (2%) patient. [296]

Lamictal (median dose 125 mg/d, range 25-300 mg/d) was used as adjunctive therapy for a median of 7 months (range, 1-24 months) in 37 children and adolescents (median age, 12 years) with refractory epilepsy and mental delay. [297] Two children experienced insomnia and/or hyperexcitation, and one patient showed psychotic-like symptoms (extreme aggressiveness, delirium) which disappeared soon after the dose of *Lamictal* was decreased. The authors noted improved attentiveness and mood in two patients. In both of these cases, *Lamictal* was added to vigabatrin (VGB, not available in the United States) and VPA.

Buchanan used *Lamictal* (mean dose 5.7 mg/kg/d, range, 0.8-10.4 mg/kg/d) adjunctively and as monotherapy to treat 34 patients (mean age 14.4 years; range, 3-26 years) with intractable epilepsy and brain damage for 1 year (range, 0.5-2 years).[298] Of children ≤14 years of age, 80% experienced an improvement in QOL characterized by parents/caregivers as increased alertness, responsiveness, and enhanced speech and mobility. In the adolescents and young adults, 77% demonstrated an improvement in quality of life (QOL) primarily characterized by increased alertness and functional independence.

6.7 Effect of *Lamictal* on Switch to Mania in Patients with Bipolar Disorder

background

Affective switch, defined as the direct transition from one mood polarity to the other, can be a characteristic of bipolar disorder, as well as an undesired effect of medications used to treat bipolar disorder. [67] *Lamictal* is not approved for the prevention of affective switch in patients with bipolar disorder.

Monotherapy

Clinical Information

In two, double-blind, placebo-controlled trials in bipolar I disorder in which patients were converted to *Lamictal* as monotherapy (100 to 400 mg/day) from other psychotropic medications and followed for up to 18 months duration, the rate of manic, hypomanic, or mixed mood episodes reported as adverse events was 5% for patients treated with *Lamictal* (n = 227) compared to 4% and 7% for patients treated with lithium (n = 166) and placebo (n = 190), respectively.[10,11]

In a combined analysis across 7 controlled monotherapy trials with *Lamictal* in patients with bipolar disorder, adverse events of mania, hypomania, and mixed mood episodes were reported in 5% of patients treated with *Lamictal* (n = 956), 3% of patients treated with lithium (n = 280), and 4% of patients treated with placebo (n = 803) (Table 26).

Table 26. Number (%) of Patients Reporting Manic, Hypomanic, and Mixed Episode Adverse Events in Controlled Monotherapy Studies* with *Lamictal* in Bipolar Disorder [206] [207] [242] [243] [245] [246] [299]

	All Mania† N (%)	Mania N (%)	Hypomania N (%)	Mixed Episode N (%)
Lamictal (N = 759)	39 (5)	25 (3)	8 (1)	6 (<1)
Placebo (N = 616)	24 (4)	16 (3)	6 (1)	4 (<1)
Lithium (N = 280)	9 (3)	8 (3)	2 (<1)	0
* Percentage is calculated using the number of subjects randomized to each treatment group in 7 controlled monotherapy studies of bipolar disorder with *Lamictal* 50-500 mg/day through 2003; † All Mania includes Mania, Hypomania, and Mixed Episodes				

In these controlled monotherapy studies of bipolar disorder, switching to mania (including mania, hypomania, or mixed episodes) was considered serious in 3% of patients in each group (*Lamictal*, lithium, and placebo) and led to withdrawal in 1% of patients in the placebo group and 2% of patients in both groups receiving *Lamictal* and lithium. [206,207,242,243,245,246,299]

Across all fixed dosage groups of *Lamictal* (Table 27), mania, hypomania, and mixed episodes were reported in 6%, 5%, and 4% of patients receiving *Lamictal* 50, 200, and 400 mg/day, respectively.

Table 27. Number (%) of Patients Reporting Manic, Hypomanic, and Mixed Episode Adverse Events by Daily Dose of *Lamictal* in Controlled Monotherapy Studies of Bipolar Disorder [206] [207] [242] [243] [245] [246] [299]

	Placebo N = 616 n (%)	***Lamictal* 50 mg N = 200 n (%)**	***Lamictal* 200 mg N = 259 n (%)**	***Lamictal* 400 mg N = 47 n (%)**	**Flexible dosing of *Lamictal* N = 253 n (%)**
All Mania*	24 (4)	12 (6)	13 (5)	2 (4)	12 (5)
Mania	16 (3)	8 (4)	11 (4)	1 (2)	5 (2)
Hypomania	6 (1)	1 (<1)	1 (<1)	0	6 (2)
Mixed Episode	4 (<1)	3 (2)	1 (<1)	1 (2)	1 (<1)
*All Mania includes Mania, Hypomania, and Mixed Episode					

Adjunctive Therapy

Controlled trials

In a multicenter, double-blind, placebo-controlled, parallel-group, flexible-dose trial, patients with bipolar I or II disorder with rapid cycling were randomized (N= 137) to adjunctive treatment with *Lamictal* (50-500 mg/d) or PBO for up to 32 weeks of treatment followed by a 2-week follow-up.[300] Following intervention for an emerging mood episode, patients could remain on double-blind treatment for the remainder of the 32-week trial, during which time *Lamictal* may have been titrated up to 500 mg/day to achieve efficacy. The rate of mania or hypomania reported as an adverse event was 9% (n = 6) for patients receiving *Lamictal* and 4% (n = 3) for placebo. A larger proportion of patients in the PBO group (65%) were receiving concomitant mood stabilizers (i.e., lithium, CBZ, VPA) compared to the group receiving *Lamictal* (60%).

Schaffer et al compared efficacy and risk of affective switch with adjunctive treatment with *Lamictal* or citalopram in a 12-week, randomized, double-blind trial in patients with bipolar I or II depression already receiving mood stabilizer(s) and experiencing depressive symptoms.[301] Mood stabilizers as monotherapy (n = 16) or polytherapy (n = 4) must have been given for at least the past 4 weeks and included lithium (n = 10), valproate (VPA, n = 9), or carbamazepine (CBZ, n = 2). Mean final doses of *Lamictal* were 100 mg/d (range 50-200 mg/d) in patients not taking VPA and 81.3 mg/d (range 25-100 mg/d) in patients taking VPA. Mean final dose of citalopram was 21 mg/d (range 10-30 mg/d). Twelve of the 20 randomized patients completed the 12-week study (*Lamictal* n = 7 and citalopram n = 5). One patient (1%) in each group experienced a switch to hypomania and discontinued study drug.

McIntyre et al compared the efficacy and tolerability of adjunctive treatment with *Lamictal* (50-200 mg/d) or venlafaxine XR (75-225 mg/d) for 8 weeks in a randomized, double-blind trial in outpatients with confirmed bipolar I or II depression. [302] Preliminary data among 20 patients reported no patient in either treatment group switched to hypomania or mania. The study is ongoing with plans to enroll 40 patients.

open-label trialS

The effectiveness of monotherapy with *Lamictal* at doses of 100-400 mg/d as maintenance treatment of bipolar I disorder was established in two multicenter, double blind, placebo controlled, 18-month studies. [12] Prior to randomization, currently or recently symptomatic bipolar I patients (N = 1315) were enrolled and *Lamictal* was initiated based on concomitant VPA or CBZ treatment or as monotherapy, titrated to a target dose, and concomitant psychotropic medications were gradually withdrawn during the 8-16 week open-label phase. The rate of mania, hypomania, or mixed episode reported as an adverse event was 3% (n = 42) during the open-label phase of these studies.[206,207]

The use of *Lamictal* as adjunctive or monotherapy for the treatment of bipolar disorder was initially studied in a 48-week, prospective, open-label, multicenter trial in 75 patients who were non-responsive or intolerant to ongoing pharmacotherapy.[303] [304] Patients received the following concomitant medications during the course of the trial: antipsychotics (n = 39), antidepressants (n = 29), lithium (n = 26), VPA (n = 22), and CBZ (n = 11). The final mean dose of *Lamictal* as monotherapy (273 mg/d) and adjunctive therapy (141 mg/d) for rapid cycling patients was lower than that for non-rapid cycling patients (375 mg/d and 193 mg/d, respectively). Four patients experienced exacerbation of mania and were hospitalized; one

of which withdrew from the study. Four patients switched from depression to mania and were hospitalized; two of which withdrew from the study.

Nolen et al conducted a 10-week, randomized, open-label study to compare the efficacy and safety of *Lamictal* (n = 11) and tranylcypromine (n = 8) in 19 adult patients (mean age 46 years) with refractory bipolar (I or II) depression.(305) After 10 weeks, responders were offered continuation treatment, while non-responders were offered crossover treatment, for an additional 10 weeks. All patients were taking a mood stabilizing medication (lithium, valproate, or carbamazepine) and did not respond or tolerate adequate trials of a conventional antidepressant. *Lamictal* was initiated at 25 mg/day for 1 week and increased weekly thereafter to a target dose of 400 mg/day (dose adjustments based on concomitant therapy). Tranylcypromine was initiated at 20 mg/day and titrated weekly to a maximum of 100 mg/day. Switch into mania was observed in two patients taking *Lamictal* and led to study withdrawal in one patient. Two patients from each group participated in the second phase and received the opposite medication. In this phase, there were no switches into mania.

retrospective review

Ghaemi et al retrospectively reviewed charts of 21 patients (mean age, 43 years) receiving combination *Lamictal* (mean dose, 179 mg/day; range 25-500 mg/day) and lithium (mean dose, 963 mg/day; 150-2000 mg/day) as long-term treatment of refractory bipolar disorder.(196) Duration of treatment averaged 55.7 weeks. Nearly half of patients (48%) discontinued the combination with lack of efficacy (19%) and activation of manic-like symptoms (19%) as the most common reasons.

7. COMPARATIVE DATA

7.1 Comparison of Pharmacokinetics and Pharmacology

Table 28. Comparison of Pharmacokinetics and Pharmacology Across AEDs

Drug*	Half-life (hours)	Bioavail-ability (%)	Protein- Binding (%)	Metabolism/Elimination
Lamotrigine	12 – 70	98	55	Major pathway: N-glucuronidation; 10% renal unchanged; > 85% hepatic
Carba-mazepine and Carba-mazepine Ex-tended-Re-lease	25 – 65 (initially) 12 – 17 (chronic)	> 75	76	Major pathway CYP 3A4, active metabolite CBZ epoxide metabolized by epoxide hydrolase; > 85% hepatic metabolism
Ethosuximide	50 – 60 (adults) 30 – 40 (children)	Not listed	0	65% hepatic metabolism by CYP 3A4 (major) and CYP 2B, 2E minor; 20% renal unchanged
Felbamate	20 – 23	Not listed	22 – 25	40% unidentified metabolism and 15% identified metabolism; 40 – 50 % renal unchanged
Gabapentin	5 – 7	60 saturable	< 3	not appreciably metabolized; renal excretion as unchanged drug
Levetiracetam and Levetiracetam Extended-Release	6 – 8	100	<10	66% renal unchanged, 24% hydrolysis
10-hydroxycarbazepine (MHD); oxcarbazepine (OXC); N-desmethylmethsuximide (NDM); cytochrome (CYP); carbamazepine (CBZ); methsuximide (MSM)				
* Based on manufacturer's full Prescribing Information				

Drug*	Half-life (hours)	Bioavail-ability (%)	Protein- Binding (%)	Metabolism/Elimination
Methsuximide	MSM: 1 – 2.6 NDM: 34 – 80 (adults); 16-45 (children)	Not listed	Not listed	Hepatic metabolism to NDM (active metabolite), NDM metabolized by CYP 2C9
Oxcarbazepine	2 OXC 9 MHD	Not listed	40 (MHD)	Cytosolic metabolism to MHD (active metabolite); MHD: 49% glucuronidation, 27% renal unchanged
Phenobarbital	53 –118 adults; 60 – 180 children	Not listed	40 – 60	Major pathway: hepatic metabolism; 25 - 50% renal unchanged
Phenytoin Phenytoin Extended-Release	7 – 42	Not listed	Highly	Not listed
Pregabalin	6	≥ 90%	0	Negligible metabolism: 90% renal unchanged
Primidone	8 –22	Not listed	20 – 25	> 40% hepatic metabolism; 40 – 60% renal unchanged
Tiagabine	4 – 9	90	96	Hepatic metabolism, major pathway: CYP 3A4; 2% excreted unchanged (25% and 63% of remaining dose excreted into the urine and feces, respectively)
Topiramate	21	80	13 –17	Not extensively metabolized: 70% renal unchanged
Valproic Acid	9 –16	Concen-tration dependent	81-90(concentra-tion dependent)	> 95% hepatic metabolism; glucuronidation (30- 50%), b-oxidation (40%), < 15-20% other oxidative mechanisms, <3% renal unchanged
Divalproex Extended-Release	9-16	~90	81-90 (concentration dependent)	Hepatic metabolism; glucuronidation (30-50%), b-oxidation (40%). <15-20% other oxidative mechanisms, <3% renal unchanged
Zonisamide	63	Not listed	40	Hepatic metabolism: acetylation (15%), reduction via CYP 3A4 (50%); 35% renal unchanged
10-hydroxycarbazepine (MHD); oxcarbazepine (OXC); N-desmethylmethsuximide (NDM); cytochrome (CYP); carbamazepine (CBZ); methsuximide (MSM)				
* Based on manufacturer's full Prescribing Information				

7.2 Comparison of *Lamictal* with Older Antiepileptic Drugs in Patients with Epilepsy

Controlled trial of lamictal, gabapentin, and carbamazepine as initial monotherapy in elderly patients

Rowan et al conducted a randomized, double-blind, parallel-group, multicenter trial comparing initial monotherapy with *Lamictal* (150 mg/day [d]), GBP (1500 mg/d), and CBZ (600 mg/d) in 593 elderly patients (mean age, 72 years) at 18 Veterans Affairs sites across the United States. [306] . Patients had ≥1 seizure(s) of any seizure type during 3 months prior to enrollment. Patients were randomized to receive monotherapy with *Lamictal* (n = 200), GBP (n = 195), and CBZ (n = 198). Dosing was as follows: *Lamictal* 25 mg/d x 2 weeks, 50 mg/d x 2 weeks, 100 mg/d x 1 week, 150 mg/d (target dose); GBP 300 mg/d x 3 days, 600 mg/d x 3 days, 900 mg/d x 3 days, 1200 mg/d x 3 days, 1500 mg/d (target dose); CBZ 200 mg/d x 2 weeks, 400 mg/d x 2 weeks, 600 mg/d (target dose). Once patients reached target dose, the dose could be adjusted as necessary.

Mean doses at 12 months were: *Lamictal* 152 mg/d, GBP 1422 mg/d, CBZ 582 mg/d. Significantly more patients receiving monotherapy with *Lamictal* (n = 111, 58%) and GBP (n = 95, 49%) remained in the trial for 12 months compared to patients receiving monotherapy with CBZ (n = 72, 37%) ($P < 0.0001$ and $P = 0.008$, respectively). The difference between *Lamictal* and GBP on this endpoint did not reach statistical significance ($P > 0.05$). Seizure-free rates at 12 months among completers were 51.4% for *Lamictal*, 47.4% for GBP and 64.3% for CBZ ($P > 0.05$). Seizure-free rates at 3 months among the intent-to-treat population were significantly better for *Lamictal* versus CBZ ($P = 0.006$). When excluding seizures during the 6-week titration period, retention was significantly better in patients receiving *Lamictal* vs CBZ at 3 and 6 months ($P = 0.001$, $P = 0.009$, respectively). Time to 1st, 2nd, 5th, 10th seizure was not statistically different between groups. Fewer patients receiving *Lamictal* terminated for adverse events versus CBZ ($P < 0.0001$) or GBP ($P < 0.015$). Statistically significant adverse events over 12 months are shown in Table Table 29.

Table 29. Statistically Significant Adverse Events over 12 Months in Rowan et al Trial [306]

	LTG	GBP	CBZ	
	N = 199	N = 194	N = 197	*P* value
	n (%)	n (%)	n (%)	
Hypersensitivity*	5 (2.7)	9 (5.1)	17 (9.9)	0.007†
Severe Hypersensitivity*	1 (0.5)	0 (0)	6 (3.5)	0.013‡
Weight Gain (>4 lbs)	87 (47.5)	120 (67.8)	88 (51.5)	0.002§ 0.001‖
Large Weight Gain (>18 lbs)	7 (3.8)	19 (10.7)	5 (2.9)	0.005§ 0.014‖
Weight Loss (> 4 lbs)	66 (36.1)	37 (20.9)	44 (25.7)	0.002‖ 0.04†
Water Retention	19 (10.4)	35 (19.8)	15 (8.8)	0.004‡ 0.02‖
Hyponatremia	12 (6.6)	7 (4)	19 (11.1)	0.014§
*Hospitalizations for hypersensitivity: CBZ (n = 7) and LTG (n = 1); †CBZ vs LTG; ‡CBZ vs GBP; §GBP vs CBZ; ‖GBP vs LTG; CBZ=carbamazepine, GBP= gabapentin, LTG=lamotrigine, lbs=pounds				

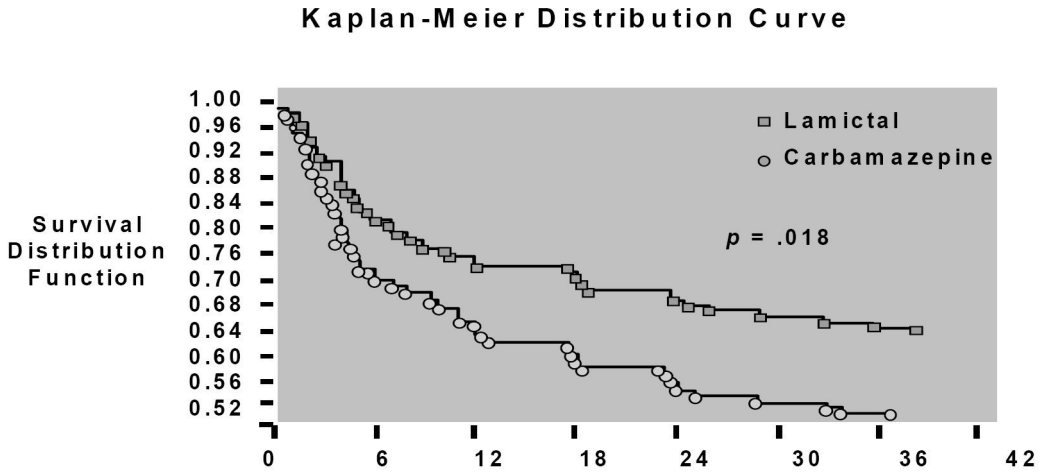
controlled trial of lamictal and carbamazepine as initial monotherapy

In a 48-week, randomized, multicenter, double-blind trial, Brodie et al compared monotherapy with *Lamictal* to monotherapy with carbamazepine (CBZ) for patients with newly diagnosed epilepsy (N = 260).[307] Patients (≥13 years old) with newly diagnosed partial seizures without secondary generalization and patients with primary or secondary generalized tonic-clonic seizures were included in the trial. Patients were randomized to receive starting doses of *Lamictal* 50 mg/d (n = 131) and CBZ 200 mg/d (n = 129). Doses were increased over 4 weeks to *Lamictal* 150 mg/d or CBZ 600 mg/d. Doses were also adjusted based on plasma concentrations (lamotrigine 2–4 mg/L, CBZ 4–10 mg/L), adverse events, or if clinically indicated during weeks 6-24. The median baseline seizure count was 4 and 3 for patients receiving *Lamictal* and CBZ, respectively.

The median daily dose for patients completing the trial was 150 mg (range, 100–300 mg) for *Lamictal* and 600 mg (range, 300–1400 mg) for CBZ. The percentage of patients seizure-free during the last 24 weeks of treatment was similar (*Lamictal*, 39%; CBZ, 38%). Overall, a greater percentage of patients with primary tonic-clonic seizures achieved seizure-control (47% for both groups) than patients experiencing partial seizures (*Lamictal*, 35% and CBZ, 37%).

The most frequently reported adverse events for patients receiving *Lamictal* or CBZ were headache, asthenia, rash, nausea, dizziness, and sleepiness. Sleepiness, which was reported more frequently by patients receiving CBZ, was the only adverse event that occurred at a significantly different frequency between the treatment groups ($P < 0.05$). More patients receiving *Lamictal* than CBZ completed the trial (65% vs 51%, $P = 0.018$) (Figure 21) and fewer patients receiving *Lamictal* withdrew from the trial due to adverse events (15% vs 27%). The most common adverse event that led to withdrawal was rash (*Lamictal*, 9%; CBZ, 13%). One patient receiving CBZ was hospitalized due to rash.

Figure 21. Time to Withdrawal from Initial Monotherapy Trial by Brodie et al for *Lamictal* and CBZ [307]



controlled trial of lamictal and carbamazepine as initial monotherapy in elderly patients

The results of a 24-week, randomized, multicenter, double-blind trial compared *Lamictal* (n = 102) and carbamazepine (CBZ; n = 48) in elderly patients (mean age 76.5 years) with newly diagnosed epilepsy.[308] *Lamictal* was dosed as follows: 25 mg QD x 2 weeks, 25 mg BID x 2 weeks, and 50 mg BID x 2 weeks. (maximum 500 mg/d). CBZ was escalated from 100 mg QD to 200 mg BID over the first 4 weeks (maximum 2000 mg/d). Doses were adjusted by the investigator according to efficacy and tolerability.

The median doses were 100 mg/d (range, 75–300) for *Lamictal* and 400 mg/d (range, 200–800) for CBZ. Median plasma concentrations of lamotrigine and CBZ at week 24 were 2.3 mg/L and 6.9 mg/L, respectively. Fewer patients receiving *Lamictal* withdrew due to adverse events compared with CBZ (18% vs 42%). The most commonly reported adverse events in patients taking *Lamictal* and CBZ included poor coordination (13% vs 17%), somnolence (12% vs 29%), dizziness (10% vs 17%), headache (9% vs 17%), constipation (9% vs 6%), vomiting (9% vs 6%), and diarrhea (7% vs 8%). Nine patients (9%) receiving *Lamictal* and 12 patients (25%) receiving CBZ experienced a rash. Fewer patients receiving *Lamictal* discontinued treatment due to rash compared with patients receiving CBZ (3% vs 19%). Three patients taking CBZ were hospitalized due to rash.

Forty patients (39%) receiving *Lamictal* were seizure-free during the last 16 weeks of the trial compared with 10 patients (21%) receiving CBZ. There was no difference in time to first seizure between groups. Overall, 71% (n = 72) of patients receiving *Lamictal* continued treatment for the duration of the trial compared with 42% (n = 20) of patients receiving CBZ. Based on the hazard ratio from the analysis of withdrawal rates, a patient treated with CBZ was more than twice as likely to discontinue treatment at any point in time compared with a patient treated with *Lamictal* ($P < 0.0001$).

controlled trial of lamictal and sustained-release carbamazepine as initial monotherapy in elderly patients

A 40-week, randomized, double-blind, parallel-group, multicenter trial compared the overall effectiveness, safety and tolerability of *Lamictal* (n = 93) and sustained-release carbamazepine (CBZ; n = 92) in newly diagnosed elderly patients (mean age 74 years) with epilepsy.[309] The mean patient age was 74 and 73 years, respectively. Doses were escalated over 4 weeks and then adjusted based clinical response. The initial, maintenance and maximum daily doses were 25 mg/d, 100 mg/d, 500 mg/d for *Lamictal* and 100 mg/d, 400 mg/d, 2000 mg/d for sustained-release CBZ, respectively.

The mean daily dose (over duration of study) was 91 mg/d for *Lamictal* and 336 mg/d for sustained-release CBZ. Completion rates were 73% for patients receiving *Lamictal* and 67% for patients receiving sustained-release CBZ. Time to withdrawal from the study due to any cause (primary endpoint) did not differ significantly between groups. More patients receiving sustained-release CBZ (89%) were seizure-free during weeks 20-40 compared to *Lamictal* (76%) on a last-observation-carried-forward

(LOCF) analysis ($P = 0.023$); however, seizure-free rates throughout the trial did not significantly differ (54% *Lamictal* vs 66% CBZ) ($P = 0.14$)

Adverse events led to discontinuation of study drug in 14% of patients receiving *Lamictal* and 25% receiving sustained-release CBZ. The most common drug-related adverse events (≥10% either group) in patients receiving *Lamictal* and sustained-release CBZ, respectively, were: dizziness (14% vs 10%), headache (11% both groups), fatigue (10% both groups), and somnolence (7% vs 10%). Unspecified rash occurred more frequently with sustained-release CBZ (13%) than *Lamictal* (5%).

controlled trial of lamictal and phenytoin as initial monotherapy

Steiner et al compared monotherapy with *Lamictal* (n = 86) to monotherapy with phenytoin (PHT, n = 95) in a randomized, double-blind, multicenter trial of patients with newly diagnosed epilepsy. [310] Patients aged 14–75 years who experienced ≥2 seizures in the previous 6 months or ≥1 seizure during the previous 3 months were included in this 48-week trial. Patients randomized to receive *Lamictal* were given 100 mg QD for the first 2 weeks and 150 mg QD for the second 2 weeks. Patients receiving PHT were given 200 mg QD for the first 2 weeks and 300 mg QD for the second 2 weeks. Following the first 4 weeks of titration, the dose of either drug could be adjusted for seizure control, adverse events and plasma drug concentrations (lamotrigine 2–4 mg/L, PHT 10–20 mg/L).

The modal and maximum daily doses were 150 mg and 400 mg, respectively for *Lamictal* and 300 mg and 600 mg, respectively for PHT. *Lamictal* and PHT were found to have similar efficacy against the seizures studied. There were no statistically significant differences in the percentages of patients remaining on each treatment and seizure-free during the last 24 and 40 weeks of the trial (Table 30).

Table 30. Percent of Patients Seizure-Free During Last 24 Weeks of Initial Monotherapy Trial by Steiner et al [310]

Seizure Type	*Lamictal* (n = 86) n (%)	Phenytoin (n = 95) n (%)	95% Confidence Interval (%)
Partial	13 (41)	13 (48)	-33,18
Secondarily generalized	6 (50)	8 (50)	-37,37
Primary generalized	19 (44)	17 (34)	-10,30
All seizure types	34 (43)	33 (36)	-8,21

The most frequently reported adverse events by patients receiving *Lamictal* and PHT included asthenia (16% vs 29), rash (14% vs 9%), headache (10% vs 19%), and dizziness (9% vs 12%). [310] For patients receiving PHT, somnolence (28%) and ataxia (12%) were also common. Adverse events considered attributable to the study drug occurred in 42% (n = 36) of patients receiving *Lamictal* and 62% (n = 59) of those receiving PHT. Thirteen patients (15%) receiving *Lamictal* and 18 patients (19%) receiving PHT withdrew due to adverse events. Rash was the most frequent single reason for withdrawal (*Lamictal*, n = 10 [12%] and PHT n = 5 [5%]). A total of 12 patients (14%) receiving *Lamictal* experienced a rash compared with 9 patients (9%) receiving PHT. There were no cases of serious rash.

There was a reduction (improvement in health-related quality of life) in the mean total Side Effects and Life Satisfaction (SEALS) score in the group receiving *Lamictal* and a slight increase in the group receiving PHT. Following a repeated measures analysis, the estimated difference between treatments compared with baseline was 4 points in favor of *Lamictal* ($P = 0.02$).

controlled trial of lamictal and valproate as initial monotherapy

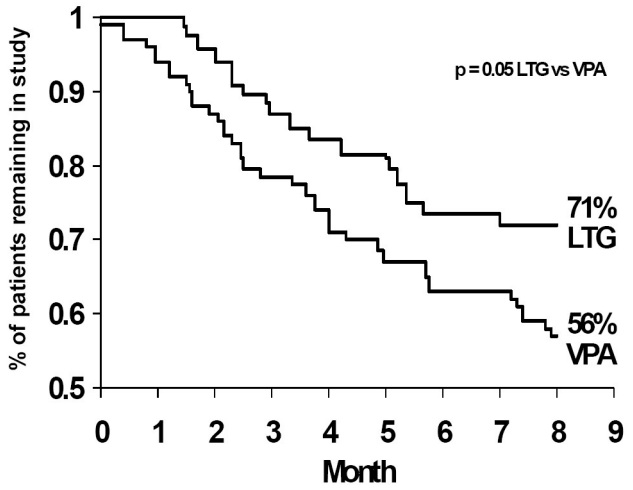
Biton et al compared the effects of monotherapy with *Lamictal* and monotherapy with valproate (VPA) on body weight in epilepsy patients ≥12 years old in a randomized, double-blind, parallel-group trial.[247] After completing a screening phase and an 8-week escalation phase, patients entered a 24-week maintenance phase. Of the 133 randomized patients, 65 patients received *Lamictal* (mean age, 34.5 years) and 68 received VPA (mean age, 30.1 years). Target maintenance doses were 200 mg/d (range 100-500 mg/d) for *Lamictal* and 20 mg/kg/d (range 10-60 mg/kg/d) for VPA, although doses were adjusted based on investigators' clinical judgement.

The mean weight change was 1.3 ± 11.9 pounds (lbs) for patients on *Lamictal* and 12.8 ± 9.3 lbs for patients on VPA. Weight gain associated with VPA was significant by week 10 and continued throughout

the trial. Twelve percent (n = 6) of patients on *Lamictal* and 62% (n = 28) of patients on VPA experienced clinically significant weight gain (i.e., >4 kg or ≥10% of baseline weight). The proportion of patients who were seizure-free during the entire trial was used for comparing the efficacy between *Lamictal* and VPA, although the trial was not powered to detect a difference in efficacy. Using this comparison, 29% of patients in the group receiving *Lamictal* and 26% of patients receiving VPA were seizure-free during the trial.

The mean time to withdrawal due to an adverse event was 103 ± 70 days for *Lamictal* and 79 ± 48 days for VPA (Figure 22). The most common (≥10%) drug-related adverse events were nausea (24%), asthenia (16%), somnolence (24%), tremor (28%), vomiting (13%), emotional disorder (10%), hair loss (10%), weight increase (10%), and appetite increase (10%) for VPA and asthenia (20%), headache (14%), nausea (12%), and dizziness (11%) for *Lamictal*. Rate of drug-related rash was 6% (n = 4) for *Lamictal* and 4% (n = 3) for VPA.[311]

Figure 22. Kaplan-Meyer Distribution Curve of Time to Discontinuation in Biton et al Trial [247]



controlled study of *lamictal* versus valproate as monotherapy

Timmings and Richens evaluated the use of *Lamictal* as a second-line monotherapy agent in 17 patients with JME who had experienced intolerable side effects (n = 2) or were uncontrolled (n = 15) with VPA. [312] Following a 4-week single-blind, placebo add-on period, patients were randomized to continue therapy with VPA or switch to *Lamictal* in a double-dummy, double-blind, 12-week study. Dosage adjustments were based on clinical status of the patient and titrated to maximums of 500 mg/d for *Lamictal* and 2500 mg/d for VPA. Patients were evaluated at 4-week intervals during the study. One patient withdrew from the study during the placebo period due to dizziness, three withdrew during crossover to *Lamictal* (n = 2 rash and n = 1 increased myoclonic jerks). No difference in seizure control was observed between the groups. In two patients, *Lamictal* suppressed electroencephalogram (EEG) photosensitivity less than VPA, but this change was not associated with seizure worsening. *Lamictal* was reported to be well-tolerated.

7.3 Comparison of *Lamictal* with Newer Antiepileptic Drugs in Patients with Epilepsy

Topiramate

Blum et al compared the cognitive effects of *Lamictal* (n = 96) versus topiramate (TPM, n = 96) as adjunctive therapy with carbamazepine (CBZ) or phenytoin (PHY) in a multicenter, double-blind, randomized study of adults (≥18 years, mean age of 40 years) with partial seizures.[258] The study was comprised of 3 phases: baseline (≥2 weeks), 8-week dose escalation, and 8-week maintenance (without dosage changes). Target maintenance doses were 500 mg/d for *Lamictal* and 300 mg/d for TPM. The primary endpoint was change from baseline to end of maintenance on a combined analysis of 6 standard measures of cognition. These tests included following domains and measures: language (Controlled Oral

Word Association Task [COWA]), reading speed and interference (Stroop Color-Word Interference), attention/vigilance (Digit Cancellation), cognitive motor speed (Lafayette Grooved Pegboard, dominant hand), memory (Rey Auditory Verbal Learning Test [RAVLT], delayed recall), timed graphomotor coding task (Symbol–Digit Modalities test [SDMT]).

Mean daily doses during maintenance were 493.6 mg for *Lamictal* and 299.3 mg for TPM. For the primary endpoint, cognitive performance at the end of the maintenance phase was better with *Lamictal* than TPM (415.3 vs 315.1; $P < 0.001$). Significant differences favoring *Lamictal* were also demonstrated for the individual tests of COWA ($P < 0.001$), Stroop Color-Word Interference ($P = 0.038$), and SDMT ($P < 0.001$). The Performance-on-Line (POL) is a computerized test simulating driving skills which monitors scanning, divided-attention, and the effective field of view. In the subset of patients administered the POL test, simulating driving skills reflected better performance with *Lamictal* than with TPM ($P = 0.021$).[259] The change in POL hard scan scores differed significantly between groups at week 8, in favor of *Lamictal* ($P = 0.033$). Additionally, at week 16, the right and left scan were significantly different between groups in favor of *Lamictal* (right $P = 0.053$, left $P = 0.004$). The median percentage change from baseline in seizure frequency was lower with *Lamictal* than with TPM during escalation ($P = 0.028$), but not during maintenance ($P = 0.062$).[258] Other seizure efficacy rates did not significantly differ between agents. The most common adverse events (≥10%) for either group (*Lamictal* vs TPM, respectively) were headache (13% vs. 24%), dizziness (19% vs 9%), nausea (11% and 6%), and fatigue (8% vs. 13%). Rash was reported by 5 patients (5%) receiving *Lamictal* and 3 patients (3%) receiving TPM. There were no serious rashes during the study. The frequencies of cognitive adverse events and of premature withdrawals related to cognitive decline were higher with TPM than *Lamictal* (6% vs 0%; $P = 0.013$).

Marson et al conducted two, prospective, open-label, controlled trials to compare standard and newer antiepileptic drugs (AEDs) as monotherapy in epilepsy. The sample population consisted of clinic outpatients in the United Kingdom, > 4 years of age, with a history of ≥ 2 clinically definite unprovoked partial (Arm A) or generalized seizures (Arm B) in the previous year (including newly diagnosed patients, patients who failed monotherapy, and patients who had achieved remission but relapsed after discontinuation of treatment). In both studies, dosing of medications was at the discretion of the clinician (aided by guidelines), with the goal of achieving seizure control with a minimum, effective dose. Follow up was conducted at 3 and 6 months, 1 year, and successive yearly intervals from the date of randomization (up to 6 years for Arm A, 7 years for Arm B). Primary outcome measures for both studies included time to treatment failure (drug discontinuation due inadequate seizure control or intolerable adverse events, or both, OR addition of other AEDs, whichever occurred first) and time to 1-year remission of seizures. Additionally, statistical analyses were performed to determine non-inferiority between new AEDs and the standard AED of the respective arm.

Arm A of the trial compared *Lamictal*, carbamazepine (CBZ), gabapentin (GBP), oxcarbazepine (OXC), or topiramate (TPM) in 1721 patients (mean age 38 years) with partial onset seizures.[313] Over the duration of the trial, patients taking *Lamictal* experienced the longest time to treatment failure for any reason compared to all other drugs. Patients taking TPM were among those with the shortest time to treatment failure for any reason. Patients taking *Lamictal* were least likely to fail treatment due to intolerable adverse events, whereas those taking TPM were most likely to fail treatment for this reason. *Lamictal* was associated with the least number of patients reporting adverse events (45%), compared to TPM which was associated with the highest number of patients reporting adverse events (53%). The most common adverse events (≥ 15%) reported by patients taking *Lamictal* were tiredness/drowsiness/fatigue/lethargy (17%) and allergic rash (15%). The most common adverse events (≥ 15%) reported in patients taking TPM were tiredness/drowsiness/fatigue/lethargy (33%), other psychiatric events (31%), weight loss (27%), depression (24%), pins/needles/dysaesthesia (24%), behavior/personality change/aggression (19%), and confusion/difficulty thinking/disoriented (19%).

Arm B of the trial compared *Lamictal*, valproate (VPA) or TPM in 716 patients (mean age 23 years) with generalized or unclassifiable epilepsy.[314] The study design of Arm B was similar to that of Arm A. For time to treatment failure for any reason, *Lamictal* was intermediate between VPA (longest) and TPM (shortest), but not statistically different from VPA. Patients taking *Lamictal* were least likely to fail treatment due to intolerable adverse events, whereas those taking TPM were most likely to fail treatment for this reason. *Lamictal* was significantly inferior to VPA for treatment failure due to inadequate seizure control, while TPM had a higher, but not statistically significant, failure rate compared to VPA. For time to

achieve 12-month remission, *Lamictal* was intermediate between VPA (statistically most effective) and TPM (least effective). Thirty-seven percent of patients taking *Lamictal* reported adverse events compared to 45% of patients taking TPM. The most common adverse events (≥ 10%) reported by patients taking *Lamictal* were allergic rash (12%) and tiredness/drowsiness/fatigue/lethargy (9%). The most common adverse events (≥ 10%) reported in patients taking TPM were tiredness/drowsiness/fatigue/lethargy (20%), behavior/personality change/aggression (18%), other psychiatric events (15%), weight loss (12%), and memory problems (10%).

Weintraub et al reviewed the charts of 1394 adult patients with epilepsy who had taken a newer antiepileptic drug (AED; US approved after 1990), including *Lamictal*, to determine the rate of psychiatric/behavioral side effects (PSE; defined as anxiety, behavioral change not otherwise specified, depression, irritability/moodiness, or psychosis).[315] In 1025 patients, the PSE was attributable to the AED. The average rate of AED-related PSEs for a single AED was 8.4%, with 6.1% leading to dosage change and 4.3% resulting in AED discontinuation. Compared to the average, signifcantly fewer PSEs were attributed to *Lamictal* (4.8%, $P = < 0.001$), with 2.4% leading to a dosage change and 1.6 leading to discontinuation of *Lamictal* ($P < 0.001$, both). A previous psychiatric condition significantly predicted AED-related PSEs.

Compared to the average, intermediate rates of PSEs were attributed to topiramate (6.3%), but this was not statistically significant, with 6.3% and 5.4% of PSEs leading to dosage change and discontinuation of topiramate, respectively.[315] See Table 31 for additional findings.

Table 31. Comparison of Average Rates of PSEs to AED-attributed PSEs in adults with epilepsy newly started on a newer AED[315]

	N	PSE % (*P*-value*)	% Cases of Dose change (*P*-value)	% Cases of Dose discontinuation (*P*-value)
Average (all AEDs)†	-	8.4	6.1	4.3
With Psych hx	-	10.8	8.6	7.4
Without Psych hx	-	7.2	4.8	2.8
Monotherapy	-	6.2	3.2	1.3
Lamictal (overall)	547	4.8 (<0.001)	2.4 (<0.001)	1.6 (<0.001)
With Psych hx	171	6.4	3.5	2.9
Without Psych hx	302	4.0 (<0.005)	1.9 (<0.005)	1.1
Monotherapy	221	5.4	1.4	0.5
TOP (overall)	112	6.3	6.3	5.4
With Psych hx	47	10.6	10.6	10.6
Without Psych hx	52	3.1	3.1	1.5
Monotherapy	16	6.3	6.3	0

*signifcance set at $P < 0.006$, only values of statistical significance are indicated as such; hx = history, PSE = psychiatric/behavioral side effects, psych = psychiatry, TOP = topiramate

†All AEDs included felbamate, gabapentin, levetiracetam, lamotrigine, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide

In a cross-sectional, multicenter study, Shechter et al compared the adverse events of *Lamictal* (n = 65) and TPM (n = 45) in children (1.5-18 years of age) with epilepsy. [316] Approximately one-third of children receiving *Lamictal* (n = 20) and half of those receiving TPM (n = 24) experienced one or more adverse events ($P = 0.03$). Regarding severity, most reactions were considered mild to moderate and none resulted in death or hospitalization. Adverse events led to discontinuation in approximately 11% and 9% of patients receiving *Lamictal* and TPM, respectively ($P = 1.0$). Adverse events generally appeared early in treatment and affected the central nervous system. The adverse events of poor appetite (13%), drowsiness (9%), speech difficulties (7%), and weight loss (7%) were observed only with TPM; while rash (6%) and headaches (5%) were observed only with *Lamictal*.

A prospective, long-term audit of *Lamictal* and TPM as add-on treatment was conducted in 55 patients with refractory epilepsy. [317] After five years of treatment, seven of 20 patients remained on *Lamictal* and 13 of 35 on TPM. Patients who continued on TPM or *Lamictal* showed an improvement in seizure frequency with seizure freedom in five of seven patients receiving *Lamictal* and four of 13 receiving TPM and 50% reduction of most severe seizure type in all seven and 10 of 13 patients, respectively. Furthermore, the quality of life assessment schedule detected a significant improvement for the patients remaining on *Lamictal* ($P < 0.01$) and TPM ($P < 0.05$).

Levetiracetam

A randomized, double-blind, multicenter trial compared behavioral changes associated with *Lamictal* (n = 132) or levetiracetam (LEV, n = 136) as adjunctive therapy in adult patients (≥16 years) with partial seizures.[285] Patients experiencing ≥2 simple or complex partial seizures with or without secondary generalization during the 6 months prior to study entry and were receiving a stable dose of carbamazepine or phenytoin with or without one other antiepileptic drug were included in the trial. Over the 8-week escalation phase, patients were titrated from an initial dose of *Lamictal* 50 mg/day to a target maintenance dose of 400 mg/day or from an initial dose of LEV 500 mg/day to a target maintenance dose of 2000 mg/day. Adjustments to the target dose were allowed during the 12-week maintenance phase to maintain seizure control or reduce adverse events. The mean change in the Anger-Hostility subscale score of the Profile of Mood States (POMS) between baseline and end of maintenance phase (primary endpoint) was -2 (±8.2) versus -0.3 (±8.4) in patients receiving *Lamictal* and LEV, respectively ($P = 0.024$). The median percent decrease in seizure frequency from baseline to end of maintenance phase was 60% with *Lamictal* and 65% with LEV ($P = 0.501$). The most common adverse events (≥10%) for *Lamictal* or LEV, respectively, were headache (32%; 25%), dizziness (13%; 15%), nausea (11%; 10%), fatigue (8%; 11%), somnolence (5%; 12%), nasopharyngitis (6%; 10%), and irritability (6%; 10%). Rash was reported in 6% of patients receiving *Lamictal* and 7% receiving LEV; no cases were serious. Eleven percent of patients receiving *Lamictal* withdrew due to adverse events versus 18% receiving LEV.

Sasso et al presented preliminary data from a 12-month trial comparing the efficacy and safety of adjunctive treatment with *Lamictal* or levetiracetam (LEV) in 40 elderly (age 65-85 years; mean 73) patients with epilepsy previously uncontrolled on AED monotherapy. [318,319] At 3 months, 5/20 (25%) patients treated with LEV (1000 to 3000 mg/d) were seizure free versus 1/20 (5%) treated with *Lamictal* (150 to 500 mg/d). Seizure reduction of ≥ 50% was reported in 14/20 (70%) patients receiving LEV and 4/20 (20%) patients receiving *Lamictal*. After 6 months, the percentage of seizure-free patients was unchanged for LEV and 2 patients treated with *Lamictal* became seizure free. The percentage of patients with ≥50% seizure reduction also remained unchanged in both groups. [318] At 12 months, 5/20 (25%) patients were seizure free with LEV compared to 2/20 (10%) of patients taking *Lamictal*. Seizure reduction of > 50% occurred in 70% (14/20) and 20% (4/20) of patients taking LEV and *Lamictal*, respectively.[319] Two patients discontinued LEV (adverse events) and 5 discontinued *Lamictal* (n = 2 lack of efficacy, n = 3 adverse events).

Sills et al presented preliminary data from a 6-week, open-label trial comparing the efficacy of monotherapy with *Lamictal* or LEV in 166 patients (age 16-99 years; median 35 years) with newly-diagnosed epilepsy.[320] Over the 6-week period, patients were titrated from an initial dose of *Lamictal* 25 mg/day to a target dose of 150 mg/day or from an initial dose of LEV 500 mg/day to a target dose of 1000 mg/day. Median daily doses at 6 weeks were 100 mg (range 50 mg – 150 mg) for *Lamictal* (n = 85) and 1000 mg/day (range 0 mg - 2000 mg) for LEV (n = 81). In the intention-to-treat analysis, 36.5% of patients randomized to receive *Lamictal* were seizure-free at 6 weeks compared to 63% of patients receiving LEV ($P < 0.005$) (primary endpoint). No adverse event data were reported.

Several retrospective reviews have evaluated retention rates of newer antiepileptic drugs, including *Lamictal* and levetiracetam (LEV), as a composite measure of tolerability and efficacy in patients with epilepsy.[321,322,323,324] Although rates varied by study, overall retention rates within each study were similar or higher for *Lamictal* compared to LEV as adjunctive or monotherapy.

Weintraub et al reviewed the charts of 1394 adult patients with epilepsy who had taken a newer antiepileptic drug (AED; US approved after 1990), including *Lamictal*, to determine the rate of psychiatric/behavioral side effects (PSE; defined as anxiety, behavioral change not otherwise specified, depression, irritability/moodiness, or psychosis).[315] In 1025 patients, the PSE was attributable to the AED. The average rate of AED-related PSEs for a single AED was 8.4%, with 6.1% leading to dosage change and

4.3% resulting in AED discontinuation. Compared to the average, signifcantly fewer PSEs were attributed to *Lamictal* (4.8%, *P* = < 0.001), with 2.4% leading to a dosage change and 1.6 leading to discontinuation of *Lamictal* (*P* < 0.001, both). A previous psychiatric condition significantly predicted AED-related PSEs.

Significantly more PSEs were attributed to levetiracetam (15.7%, *P* < 0.001 compared to the average), with 12.3 % and 8.8% of PSEs leading to dosage change and discontinuation of levetiracetem, respectively (*P* < 0.001, both).[315] See Table 32 for additional findings.

Table 32. Comparison of Average Rates of PSEs to AED-attributed PSEs in adults with epilepsy newly started on a newer AED[315]

	N	PSE % (*P*-value*)	% Cases of dose change (*P*-value)	% Cases of dose dis-continuation (*P*-value)
Average (all AEDs)†	-	8.4	6.1	4.3
With Psych hx	-	10.8	8.6	7.4
Without Psych hx	-	7.2	4.8	2.8
Monotherapy	-	6.2	3.2	1.3
Lamictal (overall)	547	4.8 (<0.001)	2.4 (<0.001)	1.6 (<0.001)
With Psych hx	171	6.4	3.5 (<0.005)	2.9
Without Psych hx	302	4.0 (<0.005)	1.9 (<0.005)	1.1
Monotherapy	221	5.4	1.4	0.5
LEV (overall)	521	15.7 (<0.001)	12.3 (<0.001)	8.8 (<0.001)
With Psych hx	169	21.3 (<0.001)	18.3 (<0.001)	15.4 (<0.001)
Without Psych hx	310	13.1 (<0.001)	9.4 (<0.001)	5.7 (<0.001)
Monotherapy	101	8.9	7.9 (<0.005)	4.0

*signifcance set at *P* < 0.006, only values of statistical significance are indicated as such; hx = history, LEV = levetiracetam, PSE = psychiatric/behavioral side effects, psych = psychiatry

†All AEDs included felbamate, gabapentin, levetiracetam, lamotrigine, oxcarbazepine, tiagabine, topiramate, vigabatrin, zonisamide

7.4 Comparison of *Lamictal* with Other Medications in the Treatment of Bipolar Disorder

Lithium

Placebo-controlled maintenance trials in bipolar I disorder

Two multicenter, double blind, placebo controlled, 18-month studies with *Lamictal* in adult patients with current or recent mood episodes (depression, mania, hypomania, or mixed episodes) associated with bipolar I disorder included lithium as an active comparator.[10,11,12] The studies were prospectively designed to be combined for a highly powered assessment of the main treatment effects of *Lamictal* and lithium and their relative efficacy on manic and depressive episodes, specifically.[12] Currently or recently symptomatic patients (N = 1305) were enrolled and received *Lamictal* during the 8-16 week open-label phase. Approximately half of patients (n = 638) were stabilized and randomized for up to 18 months of double-blind monotherapy with *Lamictal* (n = 280; 50-400 mg/d at fixed or flexible doses), lithium (n = 167; titrated to 0.8-1.1 mEq/L) or PBO (n = 191). The primary endpoint was time to intervention for a mood episode (TIME) and secondary endpoints included time to intervention for depression, time to intervention for mania, survival in study, and tolerability. The studies do not allow for rigorous comparisons of the safety and efficacy of *Lamictal* to lithium because all patients initially received open-label *Lamictal* and some were eliminated due to intolerance or lack of efficacy during this preliminary phase. Additionally, the lithium arm of one of the studies was prematurely discontinued for administrative reasons. The fact that all patients received *Lamictal* in the open-label phase confounds the comparison of adverse event rates in the double-blind phase.

In the individual studies of patients currently or recently manic/hypomanic or depressed, both *Lamictal* and lithium were superior to PBO at prolonging TIME ($P = 0.018$ *Lamictal* versus PBO, $P = 0.003$ lithium versus PBO; and $P = 0.029$ both Lamictal and lithium versus PBO, respectively).[10,11] There were no significant differences between *Lamictal* and lithium on efficacy measures.

In the combined analysis, the mean dose of *Lamictal* was 245 mg/d and the mean serum lithium level was 0.7 mEq/L. [12] Both *Lamictal* and lithium significantly delayed TIME and overall survival in study versus PBO (TIME: $P < 0.001$ for both; survival in study: $P < 0.001$ *Lamictal* versus PBO, $P = 0.006$ lithium versus PBO). An evaluation of time to the occurrence of depression or mania revealed a statistically significant benefit for *Lamictal* over PBO in delaying the time to occurrence of both depression ($P = 0.009$) and mania ($P = 0.034$), although the finding was more robust for depression. Lithium was significant over PBO on time to occurrence of mania ($P = 0.001$), but not for depression ($P = 0.120$). There were no significant differences between *Lamictal* and lithium on efficacy measures, except on time to occurrence of mania in favor of lithium ($P = 0.030$).

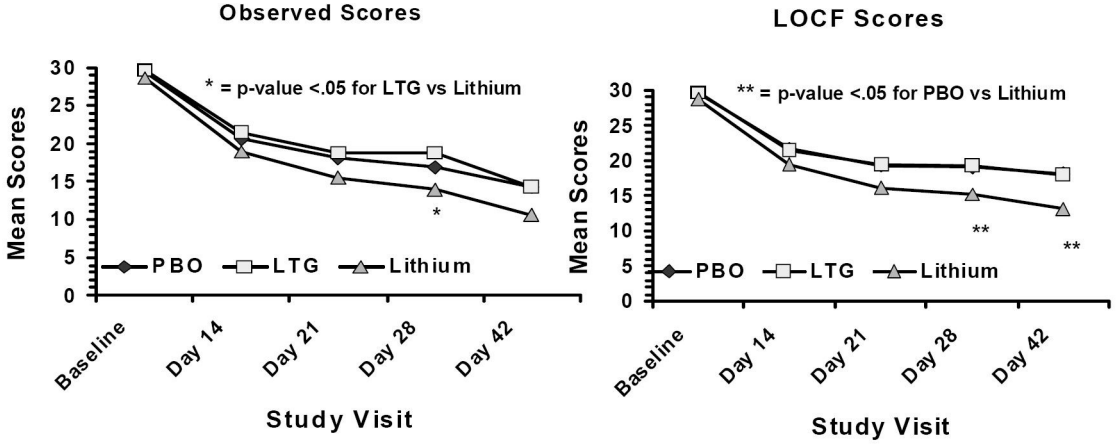
Placebo-Controlled trials in Acute mania

Acute Treatment versus Lithium

Lamictal (n = 74) as monotherapy was compared to PBO (n = 77) or lithium (n = 78; serum levels of 0.7-1.3 mEq/L) monotherapy in a 6-week, double-blind, fixed dose study of hospitalized adults (mean age, 38 years) with an acute manic or mixed episode.[299] *Lamictal* was initiated at 25 mg/day and titrated up to 200 mg/day over 6 weeks. Overall, the severity of the patients' current episode was rated as severe with psychotic features for 50% of patients.

Of the 229 patients randomized, 140 (61%) completed the study. More patients receiving lithium (n = 57, 73%) completed the study compared with patients receiving PBO (n = 46, 60%) or *Lamictal* (n = 37, 50%). The most common reasons for withdrawal were lack of efficacy (18% PBO, 11% *Lamictal*, 8% lithium), adverse events (9% PBO, 15% *Lamictal*, 10% lithium), and withdrawal of consent. Observed Mania Rating Scale (MRS-11) scores decreased from baseline to day 42 for all treatment groups (primary endpoint; Figure 23). The mean change from baseline in MRS-11 scores was numerically greater in the lithium treatment at all points after day three. Last observation carried forward (LOCF) (Figure 23) results were similar, but the lithium group experienced a statistically significantly improvement compared with the PBO group at day 42 ($P = 0.05$).

Figure 23. MRS-11 Scores for *Lamictal* versus Placebo and Lithium in Acute Mania Study (N = 228) [299]



Responders to treatment (defined as ≥50% reduction in MRS-11 scores between baseline and end of treatment) included 47%, 55%, and 62% of patients receiving PBO, *Lamictal*, and lithium, respectively.[299] Scores from the secondary efficacy variables decreased or showed improvement for all treatment groups, but statistical significance was only demonstrated at certain timepoints. Greater improvement was consistently demonstrated in patients receiving lithium.

Overall, 41 (53%), 42 (57%), and 37 (47%) of patients receiving PBO, *Lamictal*, and lithium, respectively experienced adverse events (Table 33). Mania/hypomania/mixed manic depressive episodes led to withdrawal in 14 patients (n = 2 PBO, n = 8 *Lamictal*, and n = 4 lithium). Six patients (n = 1 PBO, n = 2 *Lamictal*, n = 3 lithium) were withdrawn due to psychotic disorder, and two patients each were withdrawn from PBO and *Lamictal* for depression. Two patients on *Lamictal* and one patient on PBO were withdrawn from the study due to non-serious rash. No cases of rash were considered serious.

Table 33. Reported Adverse Events in Patients from Acute Mania Study[299]

Adverse Event	Placebo n = 77 n (%)	*Lamictal* n = 74 n (%)	Lithium n = 78 n (%)
Insomnia	3 (4)	8 (11)	0
Agitation	6 (8)	6 (8)	1 (1)
Extrapyramidal disorder	4 (5)	6 (8)	4 (5)
Headache	3 (4)	6 (8)	3 (4)
Vomiting	2 (3)	5 (7)	5 (6)
Tremor	2 (3)	5 (7)	4 (5)
All mania*	4 (5)	4 (5)	3 (4)
Mania	4 (5)	3 (4)	2 (3)
Infection	3 (4)	4 (5)	3 (4)
Diarrhea	1 (1)	1 (1)	4 (5)
*All mania includes mania, hypomania, and mixed depressive episode			

A 3-week, double-blind, randomized, study of similar design compared *Lamictal* as monotherapy with PBO or lithium for the treatment of an acute manic or mixed episode (N = 216).[246,299] The original protocol contained a lithium arm, however enrollment was discontinued after 36 subjects enrolled, thereby limited power to detect statistical differences between PBO and lithium.[246] Lithium was dosed to therapeutic levels (0.8–1.3 mEq/L) and *Lamictal* was dosed 25 mg QD for weeks 1-2 and 50 mg QD during week three.

Sixty percent (n = 130) of patients completed the study, including 61 (64%) receiving PBO, 53 (62%) receiving *Lamictal*, and 16 (44%) receiving lithium. No significant difference in efficacy was demonstrated between patients receiving *Lamictal* or PBO using the MRS-11. Observed analysis scores for MRS-11, MRS-16, Brief Psychiatric Rating Scale (BPRS), and Global Assessment Scale (GAS) suggested lithium was more effective than PBO by day 10. There was also no statistical difference between the three groups in terms of resource utilization or patient satisfaction. Two patients receiving *Lamictal* withdrew due to mania and four patients (n = 2 PBO, n = 1 *Lamictal*, and n = 1 lithium) withdrew due to non-serious rash.

Ichim et al conducted a 4-week, randomized, double-blind trial comparing *Lamictal* (n = 15) with lithium (n = 15) for the treatment of mania in patients (20-59 years) with bipolar disorder.[325] Washout period of one-day was required for other psychotropic agents. Patients were excluded if they had received a neuroleptic depot preparation within one month or fluoxetine within five weeks. Patients randomized to *Lamictal* received 25 mg QD for week one, 50 mg QD for week two, and 100 mg QD thereafter. Lithium was dosed 400 mg BID and was monitored by an independent clinician. Lorazepam, 4 to 12 mg QD, could be used as needed for aggression.

The mean BPRS score for both groups of patients significantly improved from baseline to end of treatment (52.8 to 30.2 for *Lamictal*, $P = 0.0002$ and 46.8 to 28.2 for lithium, $P = 0.0005$). Improvement from baseline was also observed using CGI-S ($P = 0.0002$ *Lamictal* and $P = 0.0005$ lithium), and CGI-I for both treatment groups. Additionally, there was improvement on the Global Assessment of Functioning (GAF) scale across both groups at the end of the trial versus baseline ($P = 0.001$ *Lamictal* and $P = 0.002$ lithium). Scores on the MRS for both treatment groups declined similarly during the trial and the scores were not significantly different on day 28 (*Lamictal* 14.3, lithium 13.2). Both groups experienced significant improvement compared to baseline on the MRS ($P = 0.0002$ *Lamictal*, $P = 0.0005$ lithium). Based on a responder analysis (≥50% reduction in MRS score and BPRS score and a CGI-S score of 1 or 2) the following results were observed: 1) MRS – 8/15 receiving *Lamictal* and 9/15 receiving lithium responded, 2) BPRS – 7/15 receiving *Lamictal* and 4/15 receiving lithium responded and, 3) CGI-S – 7/15 receiving

Lamictal and 4/15 receiving lithium responded. The mean total dose of lorazepam used during the trial did not differ between groups. No significant adverse events were observed in either group and no rashes were reported by patients receiving *Lamictal*.

Atypical Antipsychotics

OPen-label Trial

In an open-label, prospective, 16-week trial, *Lamictal* was added to mood stabilizer(s) and antidepressants in patients (mean age 39±10.7 years) with refractory bipolar I or II depression. [326] Sixty-six patients were randomized to *Lamictal* (n = 21), inositol (n = 16), or risperidone (n = 11) in addition to current treatment. *Lamictal* was initiated at 50 mg QD for 2 weeks, then increased to 50 mg BID for 2 weeks, for a final dose range of 150-250 mg/day. Target doses for inositol and risperidone were 10-25 grams and 6 mg as tolerated, respectively. Recovery was defined as ≤2 DSM-IV mood episode symptoms and no significant symptoms present for 8 weeks.

At week 8, recovery rates were as follows: 23.8% of patients receiving *Lamictal*, 17.4% of patients taking inositol, and 4.6% of patients taking risperidone (not statistically significant). Lower depression ratings, CGI-S, and Global Assessment Functioning Scale (GAF) scores were noted with *Lamictal* versus inositol and risperidone. Two patients taking *Lamictal* withdrew due to adverse events. Four patients receiving *Lamictal* switched to mania or hypomania. There were no other significant differences in adverse events between agents.

Antidepressants

controlled comparative clinical trials

Acute Treatment of Bipolar I Depression versus Olanzapine-Fluoxetine Combination

Monotherapy with *Lamictal* (n = 205) and olanzapine-fluoxetine combination (OFC) (n = 205) was compared in a randomized, double-blind, parallel-group trial with acute (7-week) and maintenance (25-week) periods in adult patients (mean age, 37 years) with acute bipolar I depression.[327,328] Patients were randomized to treatment with *Lamictal* (started at 25 mg/d and gradually titrated to 200 mg/d) or OFC (started at 6/25 mg/d and titrated up to a maximum dose of 12/50 mg/d).

Patients receiving OFC had significantly ($P < 0.05$) greater improvement in acute efficacy across the 7-week treatment period than patients receiving *Lamictal* on CGI-S (primary endpoint), MADRS, and YMRS.[327] Time to response (≥50% reduction in MADRS) was significantly shorter for OFC than *Lamictal* ($P = 0.01$). Response rates (≥50% reduction in MADRS or CGI-S ≤3) did not significantly differ between groups during the acute or maintenance periods.[327,328] Across 25 weeks of treatment, patients receiving OFC experienced significantly ($P < 0.05$) greater improvement on individual efficacy scales than patients receiving *Lamictal*, including the suicide item of the MADRS (-0.92, -0.82, respectively; $P = 0.008$).[328] Among patients who were in remission (MADRS ≤12) at the end of the 7-week acute phase (*Lamictal* 49.2% and OFC 56.4%, $P = 0.158$), relapse rates (MADRS ≥15) did not significantly differ between treatments. Rates of treatment-emergent mania also remained low and consistent between groups (*Lamictal* 7.3% vs OFC 5.0%, $P = 0.401$).

Common adverse events (≥5%) that occurred more frequently ($P < 0.05$) in patients receiving OFC versus *Lamictal*, respectively, included: increased weight (22.4% vs 2.9%), somnolence (21% vs 9.3%), increased appetite (19.5% vs 9.3%), dry mouth (17.1% vs 5.9%), sedation (14.1% vs 2.9%), tremor (10.7% vs 1.5 %), lethargy (5.9% vs 1.5%), disturbance in attention (5.4% vs 1%), and peripheral edema (5.4% vs 0%). Common adverse events (≥5%) that occurred more frequently ($P < 0.05$) in patients receiving *Lamictal* versus OFC, respectively, included: insomnia (14.7% vs 5.9%), irritability (7.4% vs 2.9%), and arthralgia (5.9% vs 1.5%). Weight gain ≥7% (33.8% vs 2.1%, $P <0.001$) and high fasting laboratory values of cholesterol ≥240 (15.9% vs 3.7%, $P < 0.001$), low-density lipoprotein cholesterol (8.9% vs 1.5%, $P = 0.006$), prolactin (18.5% vs 7.6%, $P = 0.006$), ALT (12% vs 4.9%, $P = 0.036$), and AST (8.3% vs 2.1%, $P = 0.019$) were reported in patients receiving OFC versus *Lamictal*, respectively.

Acute Treatment of Bipolar I or II Depression versus Venlafaxine XR

McIntyre et al compared the efficacy and tolerability of adjunctive treatment with *Lamictal* (50-200 mg/d) or venlafaxine XR (75-225 mg/d) for 8 weeks in a randomized, double-blind trial in outpatients

with confirmed bipolar I or II depression. [302] Preliminary data among 20 patients found a significant and comparable reduction in depressive symptoms from baseline to end of treatment for *Lamictal* and venlafaxine XR as measured by response and remission rates. Both agents were well-tolerated and discontinuation rates were similar. No switches to hypomania or mania were reported.

Acute Treatment of Bipolar I or II Depression versus Citalopram

Schaffer et al compared efficacy and risk of affected switch with adjunctive treatment with *Lamictal* or citalopram in a 12-week, randomized, double-blind trial in 20 patients with bipolar I or II depression already receiving mood stabilizer(s) and experiencing depressive symptoms (mean duration of symptoms 6.8 months).[301] Response was defined as a ≥50% decline in MADRS score from baseline to endpoint without a switch to hypomania or mania.

Demographics included mean age of 41 years (range 24-61 years); 85% female; bipolar disorder subtypes of I (n = 12), II (n = 8), and rapid-cycling pattern (n = 4). Mood stabilizers as monotherapy (n = 16) or polytherapy (n = 4) must have been given for at least the past 4 weeks and included lithium (n = 10), VPA (n = 9), or CBZ (n = 2). Mean final doses of *Lamictal* were 100 mg/d (range 50-200 mg/d) in patients not taking VPA and 81.3 mg/d (range 25-100 mg/d) in patients taking VPA. Mean final dose of citalopram was 21 mg/d (range 10-30 mg/d).

Twelve patients completed the 12-week study (*Lamictal* n = 7 and citalopram n = 5). Both treatment groups experienced significant improvement in mean MADRS scores (primary endpoint; *Lamictal* -13.3, $P = 0.001$ and citalopram -14.2, $P = 0.002$), but there was no significant differences between groups. Response rates for both groups combined increased from 6/19 (31.6%) at week 6 to 10/19 (52.6%) at week 12. One patient (1%) in each group experienced a switch to hypomania and discontinued study drug. Other adverse events led to drug discontinuation in 2 patients receiving *Lamictal* (dizziness, n = 1 and worsening symptoms, n = 1) and 4 patients receiving citalopram (worsening symptoms, n = 2; rash, n = 1; and elective gynecological surgery, n = 1).

Acute Treatment of Bipolar I or II Depression versus Tranylcypromine

Nolen et al conducted a 10-week, randomized, open-label study to compare the efficacy and safety of *Lamictal* (n = 11) and tranylcypromine (n = 8) in 19 adult patients (mean age 46 years) with refractory bipolar (I or II) depression.[305] After 10 weeks, responders were offered continuation treatment, while non-responders were offered crossover treatment, for an additional 10 weeks. All patients were taking a mood stabilizing medication (lithium, valproate, or carbamazepine) and did not respond or tolerate adequate trials of a conventional antidepressant. *Lamictal* was initiated at 25 mg/day for 1 week and increased weekly thereafter to a target dose of 400 mg/day (dose adjustments based on concomitant therapy). Tranylcypromine was initiated at 20 mg/day and titrated weekly to a maximum of 100 mg/day. More patients taking tranylcypromine completed the study (75%) compared to *Lamictal* (45%; P = NS). Reasons for drop-out in patients taking tranylcypromine were no response (n = 2) and side effects (n = 2). Reasons for drop out in patients taking *Lamictal* were no response (n =6), mania (n = 1), and side effects (n = 3). After the first treatment phase, 63% of patients taking tranylcypromine and 36% of patients taking *Lamictal* were considered responders [defined as a rating of "much" or "very much improved" on the Clinical Global Impression for bipolar illness scale and/or ≥ 50% improvement on the Inventory of Depression Symptomatology-Clinician version (IDS-C); P = NS]. Switch into mania was observed in two patients taking *Lamictal*. Two patients from each group participated in the second phase and received the opposite medication. In this phase, both patients responded to tranylcypromine and one patient to *Lamictal* and there were no switches into mania. Adverse events occurred in 80% and 70% of patients taking tranylcypromine and *Lamictal*, respectively. One patient taking *Lamictal* in the second phase experienced an itchy rash and discontinued the study.

Valproate

Yard et al conducted a 14-week, randomized, single-blind study to compare the efficacy and safety of *Lamictal* (n = 15) and valproate (VPA; n = 8) as adjunctive treatment for acute mania followed by maintenance monotherapy in 23 inpatients (ages 18 – 65 years) diagnosed with bipolar I disorder.[329] *Lamictal* was initiated at 25 mg/day and was increased to 25 mg twice daily (BID) for weeks 3 and 4, then 50 mg BID for weeks 5 and 6, to a maximum dose of 100 mg BID in weeks 7 and 8 (mean dose at week 8: 36 mg daily). VPA was initiated at 20 mg/kg and adjusted in 250 mg/day increments to achieve

a therapeutic dose of 50 – 120 mg/kg (mean dose at week 8: 1215 mg daily). To enter the 6-week maintenance monotherapy phase, patients were stable for discharge by week 8 and demonstrated a 50% reduction in baseline Young Mania Rating Scale (YMRS) score. The median time to discontinuation of treatment (primary endpoint) was longer for patients receiving *Lamictal* (12 weeks) compared to VPA (6 weeks; $P < 0.05$). Discontinuation rates were higher for patients receiving VPA (88%) compared with *Lamictal* (53%) ($P < 0.05$). Reasons for discontinuation of *Lamictal* included: non-compliance (n = 3), lack of efficacy (n = 3), withdrawal of consent (n = 1), and adverse events (n = 1). Reasons for discontinuation of VPA included: non-compliance (n = 5), lack of efficacy (n = 1), and adverse events (n = 1). Both treatment groups demonstrated an increase in mean Global Assessment Scale scores and a decrease in mean YMRS scores at the end of week 14 compared to baseline ($P < 0.05$). Information on specific adverse events was not provided.

Seventy-four patients with acute bipolar manic episodes prospectively received either *Lamictal* 25 mg twice daily (increased gradually to 100-200 mg/day) or valproate (VPA) 250 mg/day (increased gradually to 750-1000 mg/day) as an active control for 8 weeks.[330] Efficacy measures included the Bech-Rafaelson Mania Scale, Clinical Global Impression, while adverse events were evaluated with the Treatment Emergent Symptom Scale. Effective rates were 75% in the treatment group receiving *Lamictal* and 80% in the VPA group (P = NS). The most commonly reported adverse events included headache and debilitation in patients receiving *Lamictal*, and nausea and drowsiness were reported in patients receiving VPA (P = NS).

Of note, in placebo-controlled, double-blind trials of *Lamictal* as monotherapy for the acute treatment of manic episodes in adults with bipolar disorder, in which VPA was not used as an active control, there was no significant difference in efficacy between treatment with placebo and *Lamictal*.[246,299]

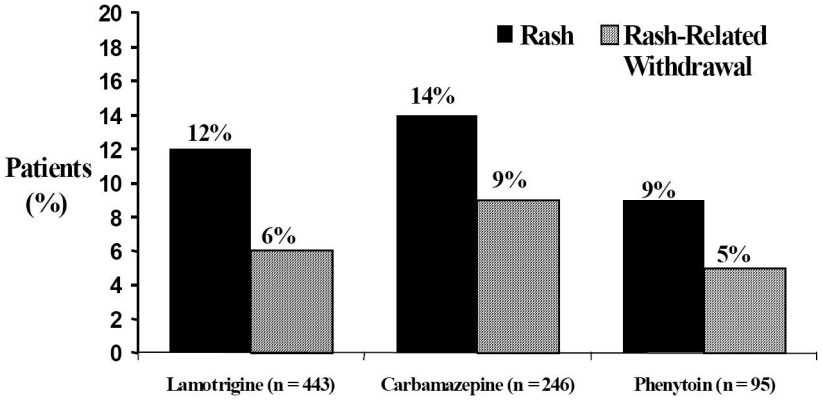
A naturalistic, cross-sectional study compared the cognitive effects of *Lamictal* (n = 38), valproate (n = 37), lithium (n = 30), oxcarbazepine (n = 19), topiramate (n = 19), and carbamazepine (n =16) in 159 patients (ages 18-70 years) with bipolar disorder.[268] Cognition was measured by a computerized neurocognitive screening battery, CNS Vital Signs, of 7 neuropsychological tests: verbal and visual memory, finger tapping, symbol-digit coding, the Stroop test, the shifting attention test, and the continuous performance test. When the scores of patients receiving *Lamictal* were compared with the other five mood stabilizers, significant differences were observed in favor of *Lamictal* in the neurocognition index, reaction time, cognitive flexibility, and complex attention. Rank order analysis indicated superiority for *Lamictal* (1.8) followed by oxcarbazepine (2.1), lithium (3.3), topiramate (4.3), valproate (4.5), and carbamazepine (5.0). There were significant differences for *Lamictal* versus carbamazepine (P = 0.004), topiramate (P = 0.019), valproate (P = 0.03), and lithium (P = 0.043).

A prospective study compared the efficacy and tolerability of *Lamictal* and valproate (VPA) in 26 patients (mean age, 45.8 years) with treatment-refractory bipolar depression.[331] They used a repeated measures linear regression (RMLR) model to adjust for severity of illness and other potential confounders while increasing statistical power. The primary outcome was prospective ratings with the Montgomery-Asberg Depression Rating Scale (MADRS). Patients were treated with *Lamictal* (mean dose of 62.5 mg/day) or VPA (mean dose of 176.6 mg/day) for a mean duration of 2.4 years. The adjusted RMLR model showed similar results between groups (MADRS mean score difference of -1.68 favoring VPA, 95% CI [-5.7 to +2.4]). Mean MADRS scores were moderately symptomatic for both groups (15.1 for *Lamictal* and 13.6 for VPA), indicating a moderate residual depression. Adverse events occurred more commonly in patients receiving VPA (12/13, 92.3%) than *Lamictal* (8/16, 50%); weight gain was the only event specifically noted.

7.5 Risk of Rash in Comparison to other AEDs

Limited data suggest that the discontinuation rates due to rash associated with *Lamictal* are similar to that reported with phenytoin (PHT) and carbamazepine (CBZ). [208] [310] [307,332] Figure 24 shows the overall rate of rash and rash-related withdrawals in the combined data from three initial monotherapy trials for *Lamictal*, CBZ, and PHT (these trials were not designed to evaluate the incidence of rash). No cases of Steven Johnson syndrome (SJS) or toxic epidermal necrosis (TEN) were reported and no patients treated with *Lamictal* were hospitalized for rash.

Figure 24. Rash Incidence: Data from 3 Monotherapy Trials* in Adult Patients with Epilepsy (208,310) (307,332)



*double-blind parallel *Lamictal* vs CBZ and *Lamictal* vs PHT; open parallel *Lamictal* vs CBZ

Arif et al retrospectively compared the relative incidence of drug-related rashes in adult patients (n = 1649) taking any of 15 most commonly used anitepileptic drugs (AEDs) [*Lamictal*, CBZ, clobazam (CLB), felbamate (FBM), gabapentin (GBP), levetiracetam (LEV), oxcarbazepine (OXC), phenobarbital (PB), PHT, primidone (PRM), tiagabine (TGB), topiramate (TPM), vigabatrin (VGB), valproate (VPA), and zonisamide (ZNS)] at an epilepsy center.(213) The overall rate of AED rash was 2.8%. Rates of rash were higher than average for patients receiving PHT (5.9%, $P = 0.0008$), *Lamictal* (4.8%; $P = 0.00095$), and CBZ (3.7%; P = NS). Rates of rash were significantly lower than average for patients receiving VPA (0.7%), LEV (0.6%), GBP (0.3%; all $P \leq 0.01$). Intermediate rates of rash were seen with CLB, OXC, PB, TGB, and ZNS. Rash rates were low (< 1% overall) with FBM and TPM, though not statistically significant. No cases of rash were seen with PRM or VGB. When repeating this analysis in patients newly started on a particular AED, significantly higher rates of rash were seen with PHT (10%), CBZ (8.7%), and *Lamictal* (6.2%; all $P < 0.01$); significantly lower rates were seen with LEV (0.8%) and GBP (0.6%; both $P < 0.025$).

8. OTHER STUDIED USES

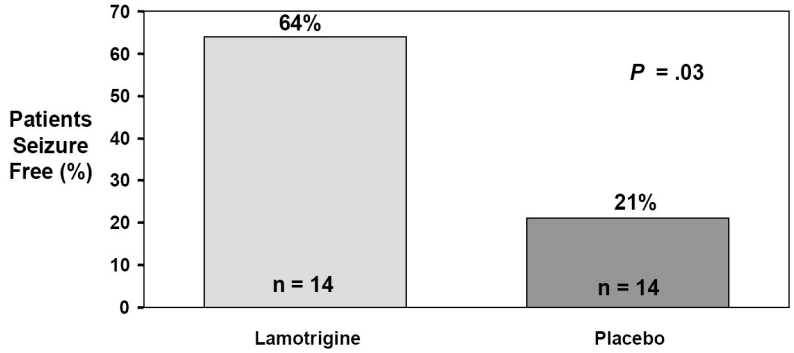
8.1 Additional Data on the Use of *Lamictal* in Children and Adolescents with Epilepsy

absence seizures: clinical studies

Frank et al evaluated the efficacy and tolerability of monotherapy with *Lamictal Tablets* in 45 children with newly diagnosed typical absence seizures. (333) The study, using a "responder-enriched" design, began with an open-label phase and was followed by a double-blind, placebo (PBO)-controlled phase. Patients (aged 2-16 years) initiated *Lamictal Tablets* 0.5 mg/kg/day (d) for two weeks followed by 1 mg/kg/d for two weeks. Doses of *Lamictal Tablets* were then increased by 1 mg/kg/d weekly until the patient became seizure-free during hyperventilation testing with electroencephalogram (EEG) recording or reached the maximum allowable dose of *Lamictal Tablets* (15 mg/kg/d). The maximum allowable dose was increased from 7 mg/kg/d to 15 mg/kg/d or an absolute limit of 1000 mg/d after 20 patients had been treated and some patients were not seizure-free, as required by the study design. Responders were then randomized to *Lamictal Tablets* (at the effective dose determined during the open-label portion, median = 5 mg/kg/d) or PBO for four weeks or until seizures, confirmed by hyperventilation testing with EEG, occurred.

Thirty of 42 patients (71%) who completed the dose escalation phase became seizure-free at a median dose of 5 mg/kg/d (range, 2–15 mg/kg/d). Eighteen of the 22 patients (82%) whose maximum allowable dose was 15 mg/kg/d became seizure-free. Twenty-eight patients entered the double-blind phase, 14 on *Lamictal Tablets* and 14 on PBO. Intent-to-treat analysis results are shown in Figure 25Figure 30.

Figure 25. Intent-to-Treat Analysis of Seizure-Free Rates in Children with Absence Seizures (333) Figure 30. Intent-to-Treat Analysis of Seizure-Free Rates in Children with Absence Seizures (333)



Drug-related adverse events reported in ≥5% of patients included abdominal pain (n = 5), headache (n = 2), nausea (n = 3), anorexia (n = 2), dizziness (n = 3), and hyperkinesia (n = 2). (333) Ten patients experienced rashes with only one case considered attributable to *Lamictal Tablets*. No patients were withdrawn due to adverse events. There were no signs of consistent changes in weight, vital signs, or clinical laboratory values.

The onset of efficacy with *Lamictal Tablets* as monotherapy was evaluated in 54 children (aged 3-13 years) with newly diagnosed typical absence seizures.(334) The study consisted of 4 phases: screening (up to 1 week), baseline (24 hours), escalation (up to 20 weeks), and maintenance (12 weeks). Twenty-eight of the 54 patients (52%) enrolled completed the study. Significantly more patients receiving *Lamictal Tablets* (56%) were seizure-free, as confirmed by hyperventilation and 1-hour electroencephalograms (EEG) during the escalation phase (primary endpoint), compared to a historical 20% rate at week 20 ($P < 0.0001$). Additionally, significantly more patients were seizure free at the end of the escalation and maintenance phases based on a 24-hour ambulatory EEG versus the historical 20% rate ($P \leq 0.001$, both).

Drug-related adverse events reported in >10% of patients included headache (n = 20), cough (n = 12), upper abdominal pain (n = 10), nasal congestion (n = 10), nasopharyngitis (n = 8), pyrexia (n = 7), and rash (n = 6). Three patients assigned to *Lamictal Tablets* were withdrawn due to adverse events, and one of those patients had an increase in seizure activity, which was reported as a serious adverse event.

JUVENILE MYOCLONIC EPILEPSY (JME)

A multicenter, open-label study evaluated the efficacy and tolerability of monotherapy with *Lamictal Tablets* in patients ≥12 years with JME who were newly diagnosed or were receiving valproate (VPA) with inadequate seizure control or unacceptable side effects. (335) (336) The study consisted of 3 phases: 1) a 2-week screening; 2) an 8-week dose escalation during which *Lamictal Tablets* was titrated up to 100-500 mg/d, per Prescribing Information and clinical response while VPA was tapered; and 3) a 24-week treatment phase during which the dose of *Lamictal Tablets* could be adjusted to achieve optimal clinical benefit.

On average, patients previously treated with VPA (n = 63) were 29 years old (range 12-50 years) and had six days per month with myoclonic seizures. During the treatment phase (n = 51), the mean dose of *Lamictal Tablets* was 314 mg/d. The majority (86%) of patients completing the study experienced no deterioration in myoclonic seizure control when switching from VPA to *Lamictal Tablets*. Most patients (63%) rated their satisfaction with *Lamictal Tablets* as monotherapy as "much better" than VPA. Approximately half (52%) of patients experienced a ≥50% reduction in days with myoclonic seizures versus baseline and 50% and 82% of patients in generalized tonic-clonic (GTC) seizures and absence seizures, respectively. At the end of the treatment phase, investigators perceived that 67% of completers showed mild, moderate, or marked improvement in global clinical status and 50% of patients had improved adverse events from baseline. The most commonly (≥10%) reported drug-related adverse events were headache (21%), dizziness (21%), tremor (11%), and rash (10%).

In the newly diagnosed patients (n = 29; mean age, 24 years [range, 12-50 years]), the mean dose of *Lamictal Tablets* was 317 mg/d (range, 100-500 mg/d). During the treatment phase, 58% of patients experienced a ≥50% reduction in days with myoclonic seizures versus baseline, and 56% and 38% of patients in the frequency of generalized tonic-clonic seizures and absence seizures, respectively. Two patients (7%) experienced an increase of >25% in myoclonus from baseline. At the end of the treatment phase, investigators perceived that 72% of patients showed mild, moderate, or marked improvement in global clinical status from baseline. The most commonly (≥10%) reported adverse events considered possibly drug-related were dizziness (17%), headache (14%), and somnolence (10%).

idiopathic generalized epilepsy

A 24-week, open-label, randomized comparison of *Lamictal Tablets* and valproate (VPA) as monotherapy was conducted in 458 newly diagnosed patients with idiopathic generalized epilepsy.(337) Of 145 pediatric patients (≥ 2 years of age), 99 were randomized to receive *Lamictal Tablets* and 46 to VPA. The primary endpoint was seizure occurrence. Baseline characteristics were similar between pediatric groups, with the exception of gender, as more males were randomized to VPA. Eighty-one percent of pediatric patients taking *Lamictal Tablets* were seizure free, compared to 84% of patients taking VPA (P = NS). Likewise, the proportion of pediatric patients experiencing adverse events was similar between groups (*Lamictal Tablets* 61%, VPA 63%). Common adverse events in the pediatric group included somnolence (*Lamictal Tablets* 4%, VPA 15%), weight increase (*Lamictal Tablets* 1%, VPA 13%), alopecia (*Lamictal Tablets* 2%, VPA 7%), and rash (*Lamictal Tablets* 12%, VPA 7%). One pediatric patient experienced serious rash. Withdrawal rates due to adverse events were 10% in patients taking *Lamictal Tablets* and 2% taking VPA. The study was terminated early due to problems with enrollment.

intractable seizures with multiple seizure types

An open-label, randomized, multicenter evaluated monotherapy in 239 newly diagnosed patients (≥12 years of age) with focal or generalized epilepsy receiving *Lamictal Tablets*, carbamazepine (CBZ), or VPA.(338) Patients with focal epilepsy were treated with *Lamictal Tablets* (n = 88) or CBZ (n = 88), those with generalized epilepsy received *Lamictal Tablets* (n = 33) or VPA (n = 30). Adolescents accounted for 14% and 3% of the groups with generalized and focal epilepsy, respectively. Median doses of *Lamictal Tablets* in adolescents were 2.1-2.4 mg/kg/d at 26 weeks. During study weeks 17 and 24, 94% and 89% of patients receiving CBZ and *Lamictal Tablets* became seizure-free according to an intent-to-treat analysis (*P* = NS). The rate of patients discontinuing treatment due to adverse events or a lack of efficacy was 19% with CBZ versus 9% with *Lamictal Tablets* (*P* > 0.05). During study weeks 17 and 24, 83% and 61% of patients receiving VPA and *Lamictal Tablets* respectively, became seizure-free (*P* = NS). The drop-out rate due to lack of efficacy or adverse events was 12% with *Lamictal Tablets* versus 3% with VPA (*P* > 0.05). Fatigue (n = 16) and rash (n = 9) were the most common adverse events in patients receiving *Lamictal Tablets*.

An open-label study evaluated the efficacy and safety of *Lamictal Tablets* (200-500 mg/d) as adjunctive therapy and conversion to monotherapy in 126 patients (ages 12-52 years; mean 23.5) with epilepsy. (339) In all patients, seizures were poorly controlled with VPA (n = 63) or CBZ (n = 63) monotherapy. The study consisted of four phases: (1) 4-week dose-escalation of *Lamictal Tablets*, (2) 8-week adjunctive *Lamictal Tablets*, (3) 8-week CBZ/VPA withdrawal, and (4) 8-week monotherapy with *Lamictal Tablets*. Of 126 patients, 107 (85%) completed dose-escalation and adjunctive therapy with *Lamictal Tablets* and 85 (68%) completed the monotherapy phase with *Lamictal Tablets*. During adjunctive therapy and monotherapy respectively, 50% and 53% patients experienced ≥50% reduction in total seizures compared to the pre-study period. Approximately 20% and 27% of patients respectively, were seizure-free during the adjunctive and monotherapy phases, respectively. Adverse events were more common during the adjunctive phase (87%) compared to monotherapy. The most common adverse events were respiratory tract infections (8.7%), dizziness (6.4%), and headache (5.6%). Treatment was discontinued in 7% of patients due to adverse events; 4% were attributed to rash.

An open-label, multicenter study evaluated the conversion from monotherapy with VPA to *Lamictal Tablets* in 84 pediatric patients (2-12 years; median duration of epilepsy three years) who had failed a previous course of VPA as monotherapy.(340) Seizure types included: partial (54%), primary generalized (45%), and unclassified (1%). Preliminary results demonstrated successful (≥ 50% reduction in seizure frequency) conversion to monotherapy from VPA to *Lamictal Tablets* in 57% patients. Mean seizure frequency was reduced from 31.2% to 10.6% during the 4-week period of monotherapy with VPA to the

4-week period of monotherapy with *Lamictal Tablets* ($P \leq 0.001$). Seizure-free rates were 45% (n = 38) during add-on and 42% (n = 35) during monotherapy with *Lamictal Tablets*. Drug-related adverse events were observed in 19% of children, primarily during add-on treatment.

Partial seizures in infants

A double-blind, placebo-controlled, responder-enriched, multicenter study investigated the adjunctive use of *Lamictal Tablets* in infants (1-24 months, median age 14 months) with partial seizures.[341] During the open-label phase, *Lamictal Tablets* was titrated to a maximum maintenance dose of 15.6 mg/kg/day (concurrent enzyme-inducing AEDs [EIAEDs]) or 5.1 mg/kg/day (no concurrent EIAEDs). In the last 4 weeks of the open-label phase (n = 172), 92 patients (53%) had a ≥50% reduction in partial seizures from baseline (49% on EIAEDs and 64% on non-EIAEDs). The proportion of subjects seizure-free during the last four weeks of this treatment phase was 23% (20% on EIAEDs and 32% on non-EIAEDs). A total of 14 subjects (8%) prematurely discontinued during the open-label phase due to adverse events; most frequently due to rash (n = 8). Forty subjects (23%) experienced a serious adverse event during the open-label phase which included complex partial seizures (3%), convulsion (2%), partial seizures with secondary generalization (2%), apnea (2%), status epilepticus (2%), pneumonia (2%), and cyanosis (2%). Rash was reported in 15% of subjects and lead to withdrawal in 5% of subjects. Serious rash was observed in one subject receiving *Lamictal Tablets* during the open-label phase but did not lead to discontinuation.

Thirty-eight subjects with a ≥40% reduction in seizure frequency from historical baseline were randomized into the double-blind phase to either continue *Lamictal Tablets* (n = 19) or gradually withdraw *Lamictal Tablets* (PBO group, n = 19) while maintaining background AEDs. The double-blind phase lasted for 8 weeks or until treatment failure (≥1 escape criteria were met). Escape criteria included: ≥ 50% increase in monthly partial seizure frequency compared with seizure frequency during the last 4 weeks of the open-label optimization period; a doubling of the highest consecutive 2-day partial seizure count observed during the open-label optimization period; onset of a new and more severe seizure type; clinically significant worsening of nonpartial seizures that were also observed during the historical baseline phase or the open-label optimization period; the need to use any therapeutic intervention in addition to study medication to control seizures; or status epilepticus. Fewer subjects receiving *Lamictal Tablets* (58%) failed treatment compared to PBO (84%) (primary endpoint, $P = 0.074$). The most frequently met escape criterion was a ≥50% increase in monthly partial seizure frequency (*Lamictal Tablets* 67%, PBO 81% of escapers). The median time to escape for *Lamictal Tablets* versus PBO was 42 and 22 days, respectively ($P = 0.059$). The difference in failure rates between treatment groups was more pronounced in the subgroup of randomized subjects who had achieved a >80% seizure reduction in the open-label phase (n = 18; 29% *Lamictal Tablets* vs. 91% PBO) based on a post-hoc analysis.

The adverse event rates during the double-blind phase were comparable across treatment groups (53% *Lamictal Tablets*, 47% PBO).[342] During the double-blind phase, one serious adverse event was reported for each treatment group (*Lamictal Tablets* - bronchitis; PBO - status epilepticus). [341]

Two hundred and six patients who completed the double-blind phase enrolled in an open-label continuation study to evaluate long-term efficacy and safety.[343] Patients were treated for 48 weeks or until their second birthday, which ever was later. Two hundred and four patients were included in the safety analysis and 199 in the intent-to-treat population.

Reductions in seizure frequency were compared to historical baseline frequencies (21/week whole sample, 28.5/week *Lamictal Tablets*-naïve patients, 21/week in *Lamictal Tablets*-experienced patients). Seizure frequency was reduced by ≥ 50% from the historical baseline in 62% of the whole sample, 60% of the *Lamictal Tablets*-naïve group, and 63% of *Lamictal Tablets*-experienced group. During the treatment phase, 13% of all patients were seizure free while 18% had an increase in seizure frequency. In the sample as a whole, the median percent reduction from baseline in partial seizure frequency was 74%.

Eighteen patients (9%) withdrew due to adverse events and 16 (8%) withdrew due to lack of efficacy. One hundred seventy-seven patients (87%) experienced ≥1 adverse event. The most common adverse events included pyrexia (n = 92, 45%), upper respiratory tract infection (n = 58, 28%), ear infection (n = 45, 22%), cough (n = 39, 19%), and vomiting (n = 37, 18%). Rash occurred in 27 (13%) patients. One patient reported serious rash, but was considered not related to *Lamictal Tablets*. Two patients experienced

serious adverse events related to *Lamictal Tablets* (status epilepticus n = 1, increased seizures n = 1). Seven patients died during the study, but none were considered to be related to *Lamictal Tablets*.

Infantile spasms (West Syndrome)

Veggiotti et al treated 30 patients with infantile spasms (1 month - 11 years) with *Lamictal Tablets* as adjunctive therapy. [344] *Lamictal Tablets* was added to ≥1 of the following AEDs whose doses remained unchanged: VPA, carbamazepine (CBZ), or vigabatrin. Following three months of treatment with *Lamictal Tablets*, five patients became seizure-free, four experienced >50% seizure reduction, 19 remained unchanged, and two experienced >50% seizure worsening. The five patients who became seizure-free (all receiving VPA), remained seizure free at a follow-up of 16–36 months (mean, 24 months). Adverse events reported with *Lamictal Tablets* included somnolence in combination with CBZ (n = 2), ataxia (n = 1), and rash (n = 1). One study reported preliminary results from 4 patients (mean age 3 years) receiving adjunctive *Lamictal Tablets* (mean dose 3 mg/kg/day) for the treatment of refractory infantile spasms. Over the study period (mean 3 months), no patient experienced a >50% seizure reduction. By parental report, 2 patients were minimally or much worse and 2 patients experienced no change.[345]

8.2 Use of *Lamictal* for the Treatment of Pain

Controlled Trials in Peripheral Neuropathy

Associated with Diabetes Mellitus

Two replicate 19-week, multicenter, randomized, double-blind, placebo-controlled studies evaluated the safety and efficacy of *Lamictal Tablets* (200, 300, or 400 mg/day [d], given twice daily) in adults with painful diabetic neuropathy (PDN, N = 360 each).[346] The studies had a 7-week dose escalation, 12-week fixed-dose maintenance, and 3-week follow-up. *Lamictal Tablets* was initiated at 25 mg/d for 2 weeks, increased to 50 mg/d for 2 weeks and subsequently titrated to 100, 200, 300, or 400 mg/d, each dose for an additional week to target dose.

A total of 222 (62%) patients completed each of the 2 studies. All groups treated with *Lamictal Tablets* reported decreased pain intensity scores at the end of treatment. In the first study, the change in an 11-point Pain Intensity Numerical Rating Scale (PI-NRS) from baseline was statistically significantly different ($P \leq 0.05$) between *Lamictal Tablets* 400 mg/d and placebo (PBO) at week 19 (primary endpoint). In the second study, the change in PI-NRS from baseline to week 19 was not statistically significant versus PBO. In both studies, change in short-form McGill Pain Questionnaire (MPQ) scores from baseline was not statistically significant between the *Lamictal Tablets* and PBO at week 8 or 19. Change in Neuropathy Pain Scale (NPS) scores from baseline was statistically significant ($P \leq 0.05$) between *Lamictal Tablets* 400 mg/d and PBO at week 8 in the first study and between *Lamictal Tablets* 300 mg/d and 400 mg/d and PBO at week 8 and between *Lamictal Tablets* 300 mg/d and PBO at week 19 in the second study. Across both studies, significant changes on other measures including post-walking pain intensity scores, change in sleep interference scores, and patient and clinician-rated global impression of change questionnaire for *Lamictal Tablets* 300 mg/d and 400 mg/d were also noted at various time points. The most common adverse events were headache (8-21% across doses and studies in patients receiving *Lamictal Tablets* vs 3 and 7% with PBO) and rash (8-16% vs 9%, respectively). One case of rash was considered serious due to hospitalization in a patient receiving *Lamictal Tablets* 25 mg/d for 10 days; however the rash resolved without complications.

Smaller controlled trials also evaluated the use of *Lamictal Tablets* in patients with PDN. Eisenberg et al conducted a randomized, double-blind, placebo-controlled, parallel-group, single-center study of 59 patients with PDN. [347] *Lamictal Tablets* at doses of 200-400 mg/d significantly attenuated PDN and had significantly superior analgesic effect on the daily NPS compared with PBO after 8 weeks of treatment. Adverse events were similar between groups and included rash, nausea, epigastric pain, headache, drowsiness, and dizziness. Jose et al compared *Lamictal Tablets* (100 mg twice daily) and amitriptyline (AMT, 50 mg at bedtime) in a 14-week, randomized, double-blind, cross-over, active-control study in 53 patients with PDN.[348] As compared with AMT, *Lamictal Tablets* was comparable on measures of efficacy using a visual analog scale (VAS) and was associated with significantly fewer adverse events.

Associated with Human Immunodeficiency Virus (HIV)

Simpson et al conducted a 12-week, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of *Lamictal Tablets* in the treatment of 227 adult patients with painful HIV-associated distal sensory polyneuropathy (DSP). [349] Patients were stratified based on exposure to neurotoxic antiretrovirals (NTOX) (*Lamictal Tablets* n = 62; PBO n = 30) or no exposure to NTOX (*Lamictal Tablets* n = 88; PBO n = 47). *Lamictal Tablets* was initiated at 25 mg every other day in patients not taking an enzyme-inducing antiepileptic drug (EIAED, e.g. carbamazepine and phenytoin) and titrated up to 400 mg/d at week 8-11. In patients taking an EIAED, *Lamictal Tablets* was initiated at 25 mg/d and titrated up to 600 mg/d.

The mean reduction from baseline to week 11 in the Gracely Pain Scale (primary endpoint) revealed no statistically significant differences between *Lamictal Tablets* and PBO in the total cohort or either subgroup. Patients randomized to *Lamictal Tablets* and taking NTOX had greater improvements in pain on the Gracely Pain Scale versus baseline and on the analysis of the slope pain scores over time than PBO ($P = 0.07$ and $P = 0.004$). Patients randomized to *Lamictal Tablets* and not taking NTOX experienced a comparable reduction in pain on the Gracely Pain Scale to that in the NTOX group. However, these differences were not significant versus PBO. Analysis of the slope of the pain scores over time showed statistical significance in favor of *Lamictal Tablets* ($P = 0.004$). Significant differences ($P < 0.05$) in pain reduction with *Lamictal Tablets* vs PBO were also reported on the VAS, MPQ, and clinician-rated relief. The most common adverse events for *Lamictal Tablets* and PBO, respectively, were rash (14%, 12%), infection (11%, 9%), nausea (11%, 10%), diarrhea (11%, 9%), and headache (11%, 10%). There were no cases of serious rash.

Simpson et al initially studied *Lamictal Tablets* for the treatment of peripheral neuropathy associated with HIV in a multicenter, randomized, double-blind placebo-controlled study of 42 patients. [350] *Lamictal Tablets* was initiated at 25 mg daily, titrated to 300 mg/d over 7 weeks, and continued treatment for 7 weeks. Of 29 patients available for analysis (*Lamictal Tablets* n = 9, PBO n = 20), patients receiving *Lamictal Tablets* reported greater reduction in pain from baseline compared to PBO using the modified Gracely scale. The adjusted (for baseline pain) mean difference in pain score was significantly improved in patients receiving *Lamictal Tablets* versus PBO ($P = 0.03$). Patients receiving *Lamictal Tablets* experienced a steeper decrease of pain scores over time than those receiving PBO ($P = 0.02$). In a retrospective, sub-group analysis, the mean baseline pain scores for patients receiving NTOX agents was significantly higher than the mean baseline scores for those not receiving NTOX, but not statistically different from PBO. However, for patients not taking NTOX agents, the adjusted mean difference in pain scores was significantly improved for *Lamictal Tablets* versus PBO ($P = 0.03$). Five patients experienced non-serious rash, 4 of which developed rash within the first 2 weeks. All rashes resolved following discontinuation of *Lamictal Tablets* .

Associated with Chemotherapy

Rao et al conducted a randomized, double-blind, placebo-controlled study to assess the efficacy of *Lamictal Tablets* as monotherapy (target dose 300 mg/d) for 10 weeks in treating moderate and severe symptoms from chemotherapy-induced peripheral neuropathy (CIPN).[351] In 125 randomized patients (80 completers), although the average scores of PI-NRS (*Lamictal Tablets* -0.3, PBO -0.5) and Eastern Cooperative Oncology Group neuropathy scale (*Lamictal Tablets* -0.4, PBO -0.3) decreased in both groups, the differences were not statistically different. The most common adverse events (≥ 5% in either group) were ataxia, dizziness, rash, fatigue, and nausea. There was no statistically significant difference between groups in the incidence of adverse events.

Associated with Multiple Causes

A 14-week, multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluated the safety and efficacy of *Lamictal Tablets* as adjunctive therapy in patients (mean age, 60 years) with neuropathic pain experiencing inadequate pain relief with gabapentin (GBP), tricyclic antidepressants (TCAs), or non-narcotic analgesics (N = 223).[352] Patients had neuropathic pain of varying etiology (PDN, postherpetic neuralgia, traumatic or surgical nerve injury, incomplete spinal cord injury, trigeminal neuralgia, multiple sclerosis, and HIV-associated neuropathic pain), an average PI-NRS ≥4 during baseline for study inclusion, and must have received stable treatment for ≥4 weeks prior to baseline and

throughout the study with either GBP (900-3600 mg/d), a TCA (25-100 mg/d), or a single non-narcotic analgesic. The study phases included 8-week dose escalation/adjustment and 6-week maintenance. During the maintenance phase, patients received flexible doses of 200, 300, or 400 mg/d of *Lamictal Tablets* , based on tolerability, or PBO. A total of 142 patients (PBO n = 78, *Lamictal Tablets* n = 64) completed the study. The mean change on the 11-point PI-NRS (primary endpoint) from baseline to treatment week 14 (primary endpoint) in patients receiving *Lamictal Tablets* was not statistically significant versus PBO (-2.1 both, $P = 0.67$). Differences in other efficacy endpoints also did not reach statistical significance compared with PBO. The most common adverse events (≥ 5% in both groups) for *Lamictal Tablets* and PBO included dizziness (9% vs 10%, respectively), rash (18% vs 13%), and somnolence (6% vs 2%). No serious rashes were reported.

In a randomized, double-blind, placebo-controlled study, McCleane et al evaluated the analgesic potential of *Lamictal Tablets* in patients with intractable neuropathic pain (N = 100, mean age 46 years). [353] *Lamictal Tablets* was initiated at 25 mg daily for 2 weeks, followed by 50 mg daily for 2 weeks, 100 mg daily for 1 week, 150 mg daily for 1 week and 200 mg daily for the remainder of the study. Efficacy was based on patient evaluations of pain and quality of life measures using a VAS from 0-10. There was no a significant change in mean scores of any variable at week 8 compared with mean baseline for either group and no patient achieved a 50% reduction in pain. Adverse events leading to discontinuation (n = 12) included nausea, rash, and bad taste of tablets. Six patients withdrew due to lack of pain relief and 8 patients had inadequate follow-up.

Controlled Clinical Trials for Migraine Prophylaxis

Steiner et al evaluated *Lamictal Tablets* for the prophylaxis of migraine in a randomized, double-blind, placebo-controlled, parallel trial in 110 patients with recognizable attacks of migraine. [354] Following a 1-month, single-blind, placebo the run-in period, patients were randomized to receive either *Lamictal Tablets* 200 mg/day [d] (n = 37) or placebo (n = 40). Due to a high incidence of rash in patients receiving *Lamictal Tablets*, the protocol was amended to initiate *Lamictal Tablets* at 25 mg/d for weeks 1-2; 50 mg/d during weeks 3-4, and; 200 mg/d during week 5 and after (n = 19). Patients were permitted to continue current medications not known to affect migraine as well as medications for acute migraine attacks.

Efficacy was based on attack frequencies, severity of individual attacks using a standard scale of 1-3, and numbers of doses of medications used to treat acute attacks (Table 34).

Table 34. Efficacy Results for *Lamictal Tablets* in Controlled Migraine Prophylaxis Trial [354]

Efficacy Measure	***Lamictal Tablets*** **n = 37**	**Placebo n = 40**
Absolute migraine reduction* by final month	0.4 attacks/month	1.4 attacks/month
% migraine reduction* from baseline	11%	32%
Mean days affected per 28 days	4.4 days	6.9 days
Mean total severity scores per 28 days	9.6	13.1
Mean analgesic doses consumed during final month	17.8	19.9
* There was a higher baseline attack frequency in the placebo group, but the mean frequency of attacks was similar for both groups during the last 4-week period		

Fifty-three patients completed the trial; while 11 withdrew due to adverse events (*Lamictal Tablets*, n = 8; placebo, n = 3), 4 due to lack of efficacy (*Lamictal Tablets*, n = 2; placebo, n = 2), 8 for unrelated reasons, and one due to a protocol violation. Of the 18 patients who received a fixed dose (200 mg/d) of *Lamictal Tablets*, 39% (7/18) developed rash and one experienced dizziness which led to discontinuation. For patients receiving a slow dose-escalation of *Lamictal Tablets*, 21% (4/19) experienced a rash, but only one withdrew due to rash. One placebo-treated patient withdrew due to rash.

Gupta et al compared the efficacy and safety of low-dose *Lamictal Tablets* and topiramate (TPM) for prophylaxis of frequent migraine headaches (>4 attacks per month) in a single-center, double-blind,

randomized, placebo-controlled, cross-over trial of 60 patients (47 females, 13 males) in India. [355] Patients received *Lamictal Tablets* or TPM dosed 50 mg/d or PBO in divided doses for 1 month in 4 phases with a 7-day washout period between treatments. Response (50% reduction in mean migraine frequency and intensity) based on intent-to-treat analysis was the primary efficacy measure.

Of 57 patients in the intent-to-treat population, 4 withdrew at various phases; none due to adverse events. Responder rates for migraine frequency and intensity were significantly higher for *Lamictal Tablets* and TPM versus PBO (63% vs. 46% [$P = 0.02$] and 63% vs. 30% [$P < 0.001$], respectively for frequency; and 50% vs. 41% [$P = 0.01$] and 50% vs. 10% [$P < 0.001$], respectively for intensity). *Lamictal Tablets* was associated with benefits on reduction in mean monthly migraine frequency and migraine-associated symptoms ($P < 0.017$). Adverse events were not significantly different between treatment groups.

Trigeminal Neuralgia (TN)

Zakrzewska et al studied *Lamictal Tablets* as adjunctive treatment of refractory TN in a randomized, double-blind placebo-controlled, crossover study in 14 patients (44-75 years). [356] *Lamictal Tablets* was added to existing regimens of carbamazepine (CBZ) and/or phenytoin (PHY). Doses were initiated at 50 mg/d and titrated to 400 mg/d over four days. Patients received *Lamictal Tablets* or PBO for 14 days followed by a 3-day washout period and the alternative medication for an additional 14 days. Efficacy was based on patient preference that included: 1) total pain score; 2) global evaluation, and; 3) need for escape medication (increased dosages of PHY or CBZ). The primary outcome measure was a composite measure (composite efficacy index, CEI) derived from assigning greater efficacy for one treatment compared with the other for each individual patient. Based on analysis of the CEI, *Lamictal Tablets* was superior to PBO ($P = 0.011$). Global evaluations also suggested that patients felt better while receiving *Lamictal Tablets* compared with PBO ($P = 0.025$). Patients receiving *Lamictal Tablets* reported increased ability to wash their face, comb their hair, and brush their teeth. One patient in the PBO group withdrew from the study due to uncontrollable pain. The most common adverse events reported with *Lamictal Tablets* were dizziness, constipation, nausea, and somnolence.

Stiles at al conducted a randomized, double-blind, placebo-controlled study to evaluate the efficacy of *Lamictal Tablets* as adjunctive therapy in 20 patients with suboptimally controlled trigeminal neuralgia.[357] Patients were titrated over 2 months to *Lamictal Tablets* 400 – 700 mg/day (depending on concomitant medications, tolerability, and resolution of pain) or placebo. Fourteen patients completed the study. Prelimary results indicated that 3 of 7 patients taking *Lamictal Tablets* became pain free compared to 2 of 7 patients taking placebo. Two patients taking *Lamictal Tablets* had 75% reduction in number of pain attacks compared to 3 patients taking placebo who experienced 50-75% improvement. Two patients taking *Lamictal Tablets* remained unchanged, and 2 patients taking placebo worsened. No adverse event information was available in this preliminary report.

Pakdaman et al evaluated *Lamictal Tablets* as adjunctive treatment of refractory TN in a single-blind, crossover, placebo-controlled, multi-center study in 100 patients. [358] *Lamictal Tablets* 50 mg/d, *Lamictal Tablets* 100 mg/d or PBO was titrated and added to existing regiments for up to 6 months. According to preliminary results, significant improvement was noted on the present pain intensity questionnaire in patients receiving *Lamictal Tablets* 100 mg/d compared to *Lamictal Tablets* 50 mg/d or PBO ($P < 0.001$). A 62% reduction in severity and 58% reduction in the frequency of attacks were demonstrated in patients receiving *Lamictal Tablets* 100 mg/d.

Central Pain

In a randomized, double-blind, placebo-controlled, cross-over study, Vestergaard et al evaluated the use of *Lamictal Tablets* in 30 patients with central poststroke pain (CPSP) (median age, 59 years; median pain duration two years). [359] The study consisted of two eight-week treatment periods separated by a two-week washout. *Lamictal Tablets* was initiated at 25 mg/d gradually increased to 50 mg/d, 100 mg/d, and ended at 200 mg/d. Among 27 intent-to-treat patients, *Lamictal Tablets* 200 mg/d significantly reduced the median pain score (primary endpoint) to five (on an 11-point Likert scale) versus seven during PBO treatment ($P = 0.01$). No significance was achieved at doses ≤100 mg/d. Twelve patients (44%) were classified as responders. Statistical significance was achieved on secondary measures of global pain rating of physical pain ($P = 0.02$) and evoked pain by acetone drop ($P = 0.01$). *Lamictal Tablets* was

considered well-tolerated. Two non-serious rashes occurred during treatment with *Lamictal Tablets* with one leading to drug discontinuation.

In a randomized, double-blind, placebo-controlled, cross-over pilot study, Breuer et al evaluated the use of *Lamictal Tablets* in 12 patients with central pain due to multiple sclerosis (mean age, 49 years).[360] The study consisted of two thirteen-week treatment periods separated by a two-week washout. *Lamictal Tablets* was initiated at 25 mg/d gradually titrated based on pain relief and tolerability (range 50 - 400 mg/d). No study outcome related to pain was statistically significant among the 11 patients completing the study. The rate of responders was numerically greater with *Lamictal Tablets* (5/11) versus PBO (2/11). *Lamictal Tablets* was considered well-tolerated. One patient developed non-serious rash unrelated to *Lamictal Tablets*. One patient in each treatment group (*Lamictal Tablets* n = 1, PBO n = 1) discontinued the study due to adverse events.

Postoperative Pain

Bonicalzi et al evaluated the effect of *Lamictal Tablets* on postoperative analgesic requirements in a randomized, double-blind, placebo-controlled pilot study of 30 patients undergoing transurethral prostatectomy under spinal anesthesia (SA).[361] Patients received either PBO or *Lamictal Tablets* 200 mg one hour prior to SA. Both groups received a continuous intravenous infusion of 250 mL of 5% glucose with 0.3 mg of buprenorphine at 20 mL/hour at the end of the procedure. Diclofenac was administered IM for additional pain relief. VAS scores 12 hours following surgery were zero in both groups of patients; however, VAS scores were significantly lower for patients receiving *Lamictal Tablets* compared with PBO at two ($P = 0.04$), four ($P < 0.01$), and six ($P = 0.04$) hours after surgery. None of the patients who received *Lamictal Tablets* preoperatively received diclofenac postoperatively. Seven patients who received PBO requested diclofenac (n = 5, 1 injection; n = 2, 2 injections). The only reported adverse event was mild rash (n = 1) that occurred four hours after administration of *Lamictal Tablets*.

Sheen et al prospectively studied the effect of premedication with *Lamictal Tablets* on postoperative pain and analgesia in 40 patients after laparoscopically assisted vaginal hysterectomy with general anesthesia.[362] Patients were randomized 1:1 to receive *Lamictal Tablets* 300 mg or PBO two hours before surgery. Pain was assessed on a visual analogue scale (VAS) at intervals of 0-6, 6-12, 12-18, and 18-24 hours after surgery, both at rest and with activity. Preliminary data report that patients who received *Lamictal Tablets* had lower VAS scores at all time intervals. Total morphine consumption the first 48 hours after surgery was also significantly less in patients receiving *Lamictal Tablets* compared with PBO (mean of 10.2 mg vs 19.8 mg; $P \leq 0.05$).

Post-Polio Syndrome

On et al studied the effects of *Lamictal Tablets* on symptomatic relief and quality of life associated with post-polio syndrome in a randomized, double-blind, placebo-controlled study.[363] Patients (mean age, 36 years) were randomized to *Lamictal Tablets* (n = 15) or PBO (n = 15). At baseline, patients reported symptoms of fatigue, new weakness, cramps, pain at the lower extremities, cold intolerance, and sleep disturbance. *Lamictal Tablets* was started at a dose of 50 mg/d and increased to 100 mg/d after 2 weeks. All patients were given interventional advice and home exercises. Patients rated the severity of pain, fatigue, and muscle cramps on a VAS; and level of fatigue using Fatigue Severity Scale (FSS). There were statistically significant improvements from baseline on mean scores of VAS and FSS, and measures of quality of life using the Nottingham Health Profile at 2 weeks and 4 weeks in patients receiving *Lamictal Tablets*. No significant improvements were reported in patients receiving PBO. No adverse events were reported with *Lamictal Tablets*.

Sciatic Pain

Eisenberg et al evaluated *Lamictal Tablets* in an open-label study of 14 patients (24-73 years of age) with sciatica. [364] After a one-week washout period from analgesics, *Lamictal Tablets* was gradually titrated from 25 to 400 mg/d and maintained for an additional four weeks. Spontaneous pain, the Short Form McGill Pain Questionnaire (SFMPQ), the Straight Leg Raise (SLR) test, and range of motion of the lumbar spine (leaning foreword, to the affected side) were used to assess efficacy. Seven patients completed the entire treatment period. All outcome measures improved compared to baseline during the titration period, but reached a statistically significant level of improvement only at the 400 mg dose ($P <0.05$). A linear correlation was found between mean lamotrigine plasma concentration with mean dose

of *Lamictal Tablets*, mean weekly spontaneous pain (NPS and VAS), mean SLR, and mean bending the affected side. Adverse events included dizziness (n = 3) and diarrhea (n = 1) and resolved after discontinuation of *Lamictal Tablets*.

Pelvic Pain

Meltzer-Brody et al evaluated the efficacy of *Lamictal Tablets* for the treatment of chronic pelvic pain (CPP) of > 6 months duration and associated mood symptoms in an open-label, pilot study of 31 women (mean age, 41 years).[365] *Lamictal Tablets* was titrated up to 400 mg/d over 8 weeks, maintained from week 8-12, and then gradually discontinued between weeks 12-14. Patients completed the McGill Pain Scale and were administered the Hamilton Depression Scale (HAMD). The mean daily dose of *Lamictal Tablets* was 340 mg at week 8 and 367 mg at week 12. Preliminary results revealed a statistically significant change from baseline in overall reduction in McGill Pain Scale scores, pain intensity, and HAMD scores at weeks 8 (n = 31) and 12 (n = 21; $P < 0.05$, both) in the total sample. Patients with vulvodynia-type pelvic pain (n = 30) had the most robust reductions in McGill Pain Scale scores, pain intensity, and HAMD scores at both timepoints ($P < 0.05$) compared with other types of CPP (e.g., diffuse abdominal or neuropathic pain). Adverse events were not discussed by the investigators.

8.3 Use of *Lamictal* for Treatment of Rapid Cycling Bipolar Disorder in Adults

Clinical information

The effectiveness of monotherapy with *Lamictal* (100-400 mg/day) as maintenance treatment was established in two placebo-controlled 18-month trials which included a cohort of patients (30% of 404 patients in Study 1 and 28% of 171 patients in Study 2) with rapid cycling bipolar disorder (defined as 4 to 6 episodes per year).[10,11] In a combined analysis of the two studies, *Lamictal* was associated with statistically significant differences versus placebo (PBO) on delaying time to intervention for a mood episode (TIME) and overall survival in study (TIME plus discontinuation for any reason).[12] Within the subpopulation of enrolled rapid cyclers (n = 169), TIME did not significantly differ between treatment groups, although both *Lamictal* and lithium were associated with greater improvements in survival in study versus PBO ($P = 0.077$).

controlled trials

Monotherapy Trial as Maintenance of Bipolar I or II Disorder

Calabrese et al investigated the use of *Lamictal* as monotherapy as maintenance treatment of rapid-cycling in a double-blind, flexible-dose, placebo-controlled study of adults with a diagnosis of bipolar I (n = 225) or II (n = 98) disorder. [366] Patients entered a preliminary phase while experiencing any mood episode or euthymia. During the 8-12 week open-label phase, *Lamictal* was titrated over six weeks to 200 mg QD using the following schedule: 25 mg/d for weeks 1-2, 50 mg/d for weeks 3-4, and 100 mg/d at week 5. Doses could be increased at weekly intervals of 100-300 mg/d during the open-label phase. Doses were adjusted for concomitant valproate (VPA) or carbamazepine (CBZ). After ≥4 weeks of *Lamictal*, patients meeting wellness criteria had psychotropic medications tapered and discontinued.

Patients were eligible for randomization to the 6-month double-blind phase if they had 1) a minimum of *Lamictal* 100 mg/d, 2) a score of ≤14 on the Hamilton Rating Scale for Depression (HAMD) 17 items, 3) a score of ≤12 on the Mania Rating Scale (MRS) from the SADS-Change version over a 2-week period, 4) no change in dose of *Lamictal* during the final week of the open phase, 5) no mood episodes requiring additional medications or ECT after the first four weeks of the open phase. During randomization, patients were stratified by diagnosis of bipolar I or II disorder. Patients were immediately started on once daily dosing of PBO or *Lamictal* at the beginning of the double-blind phase. There was flexible dosing during the double-blind phase allowing 100-500 mg/d of *Lamictal*.

One hundred seventy-seven patients (PBO n = 87, *Lamictal* n = 90) were included in the efficacy analysis of the double-blind phase. The mean daily dose of *Lamictal* during the open and double-blind phases was 108.5 mg/d (range, 0–400 mg/d) and 287.9 mg/d (range, 100–506 mg/d), respectively. Time to intervention for a mood episode (TIME, primary endpoint) did not differ significantly between the two treatment groups ($P = 0.177$) with 50% (n = 45) on *Lamictal* and 56% (n = 49) on PBO given additional treatment. However, when discontinuing the study for any reason (study survival), a post-hoc efficacy analysis of the primary endpoint, was evaluated, statistical significance in favor of *Lamictal* was achieved

($P = 0.037$). Most patients requiring treatment experienced depressive symptoms (80%) versus manic, hypomanic, or mixed symptoms (20%).

Survival analyses performed for the subtypes of bipolar disorder did not demonstrate significant differences between those receiving *Lamictal* or PBO, although for the subtype of bipolar II disorder (BPII), there was a trend toward statistical significance between the groups for TIME ($P = 0.073$) (Figure 26). Median survival time for BPII favored *Lamictal* with 17 weeks versus seven weeks for the PBO group ($P = 0.015$). Overall, a significantly greater proportion of patients receiving *Lamictal* (41%, 37/90) compared with those receiving PBO (26%, 23/87) completed the 6-month randomized phase without evidence of relapse ($P = 0.03$) (Figure 2). Significance was also achieved for BPII with 46% of patients on *Lamictal* versus 18% on PBO stable without relapse for six months ($P = 0.04$) (Figure 27).

Figure 26. Efficacy Data for Long-Term Treatment of Rapid-Cycling Bipolar Disorder [366]

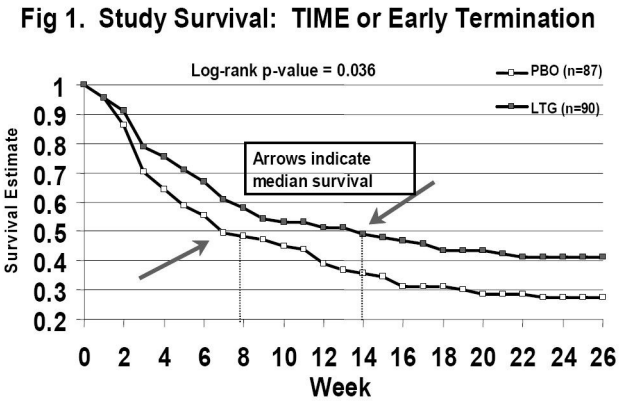
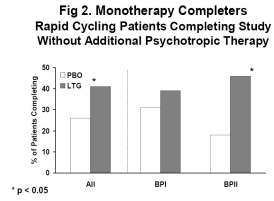


Figure 27. Efficacy Data for Long-Term Treatment of Rapid-Cycling Bipolar Disorder [366]



The Clinical Global Impressions Scale for Severity (CGI-S) scores during the double-blind phase failed to show a difference between those receiving *Lamictal* or PBO for the total study population and for the subtype of bipolar I disorder (BPI). [366] Results from Global Assessment Scale (GAS) scores were similar with significant differences favoring *Lamictal* for bipolar II disorder (BPII) at weeks 3, 6, and 12, but no significant differences for bipolar I disorder (BPI) or for the total study population.

During the open-label phase, the most common adverse events (≥10%) were headache (35%), infection (13%), influenza (10%), nausea (15%), dream abnormality (10%), dizziness (11%), and rash (14%). Twenty-five cases (8%) of rash were considered drug-related; *Lamictal* was discontinued in 15 of these cases. In the double-blind phase, the most common adverse events reported by patients receiving *Lamictal* or PBO, respectively included, headache (23% vs 17%), nausea (14% vs 11%), infection (12% vs 11%), pain (10% vs 8%), and accidental injury (11% vs 5%). None of the three (3%) rashes reported during this phase were considered to be drug-related. No serious rashes were reported. No serious psychiatric adverse events were reported during the randomized phase. The mean weight from screen to end of study for completers receiving *Lamictal* as monotherapy was unchanged. During the randomized phase, the PBO completers (n = 35) had a mean weight loss of 0.3 kg, and the completers receiving *Lamictal* (n = 35) had a mean weight gain of 1.1 kg.

In a secondary analysis of the study, Goldberg et al examined prospective Life Chart Method (LCM) data for 182 randomized patients. [367] Patients taking *Lamictal* spent significantly more days per week euthymic versus PBO ($P = 0.014$). Results were similar between patients with BPI and BPII.

Adjunctive Trial as Maintenance of Bipolar I or II Disorder

In a multicenter, double-blind, placebo-controlled, parallel-group, flexible-dose trial, patients with bipolar I or II disorder with rapid cycling were randomized to adjunctive treatment with *Lamictal* (50-500 mg/d) or PBO for up to 32 weeks of treatment followed by a 2-week follow-up. [300] Following intervention for an emerging mood episode, patients could remain on double-blind treatment for the remainder of the 32-week trial, which may have included *Lamictal* up to 500 mg/d to achieve efficacy.

Of the 137 randomized patients, 82 patients completed the trial. Time to intervention for mood episode (primary endpoint) was not statistically significant between treatment groups. However, two secondary endpoints, relapse to depression and time to depression were significant for *Lamictal* versus PBO (P = 0.007 and P = 0.047, respectively). The time to mania analysis showed statistical significance for PBO versus *Lamictal* (P = 0.032); however, the relapse to mania analysis did not show a statistically significant difference between treatment groups. For the psychiatric rating scales, there was no sustainable difference between groups.

The most commonly reported adverse events (≥10% in either group) which were more common with *Lamictal* than PBO included dizziness, back pain, pain, and pharyngitis. Dermatologic adverse events were reported in 25% of PBO-treated patients versus 22% with *Lamictal*. Twelve percent of patients withdrew due to adverse events (10% PBO and 15% *Lamictal*). Non-serious rash was the most common adverse event leading to discontinuation (3% across both groups). No serious rashes were reported. Slightly more patients reported "all mania" with *Lamictal*; while, slightly more patients reported "all depression" with PBO.

initial open-label Study

The use of *Lamictal* as adjunctive or monotherapy for the treatment of bipolar disorder was initially studied in a 48-week, prospective, open-label, multicenter trial in 75 patients who were non-responsive or intolerant to ongoing pharmacotherapy. [303,304] Dosing of *Lamictal* was based upon concomitant medications (valproate [VPA], hepatic enzyme inducers [i.e. carbamazepine (CBZ)], any other medications, or monotherapy). *Lamictal* as monotherapy or given with any drug except hepatic enzyme-inducers or VPA was dosed 25 mg QD for weeks 1 and 2, 50 mg QD for weeks 3 and 4, and 100-200 mg QD (maximum of 500 mg/d) for weeks 5-48. When used adjunctively, doses were halved with VPA and doubled with hepatic enzyme-inducers. Patients received the following concomitant medications during the course of the trial: antipsychotics (n = 39), antidepressants (n = 29), lithium (n = 26), VPA (n = 22), and CBZ (n = 11).

Of the 41 patients who met criteria for rapid cycling, 32% received *Lamictal* as monotherapy versus 6% of the non-rapid cycling patients. The final mean dose of *Lamictal* as monotherapy (273 mg/d) and adjunctive therapy (141 mg/d) for rapid cycling patients was lower than that for non-rapid cycling patients (375 mg/d and 193 mg/d, respectively). The average duration of study participation was less for rapid cycling patients versus non-rapid cycling patients (P = 0.12). Withdrawal due to lack of efficacy was 22% in rapid cycling versus 6% in non-rapid cycling patients. Significant improvement from baseline was demonstrated in observed scores for MRS (manic/hypomanic/mixed at entry), HAMD (depressed at entry) and GAS (all patients) at every timepoint (P < 0.05). Rapid cycling patients had significantly less improvement on the MRS (LOCF at week 48) and GAS scores than non-rapid cycling patients. Depression ratings did not vary significantly between groups. There were fewer rapid-cycling patients compared with non-rapid cycling entering the study in manic, hypomanic, or mixed episodes who achieved ≥50% improvement on the MRS (57.6% vs. 90.5%, P = 0.01). However, marked improvement on the HAMD ≥50% was similar between the two groups (47.6% vs. 47.4%, respectively). Marked improvement on the GAS (≥10 point increase) was present in 49% of rapid cycling and 69% of non-rapid cycling patients (P = 0.10).[304]

Four patients experienced exacerbation of mania and were hospitalized; one of which withdrew from the study.[303] Four patients switched from depression to mania and were hospitalized; two of which withdrew from the study. The most frequently reported adverse events were dizziness (29%), tremor (23%) somnolence (21%), headache (19%), non-serious rash (15%), nausea (15%), and insomnia (13%). The most frequent adverse events leading to discontinuation of *Lamictal* were non-serious rash (n = 7, 9%), nausea (n = 1, 1.3%), somnolence (n = 1, 1.3%), and tremor (n = 1, 1.3%).

Open-Label study versus lithium

Walden et al conducted an open-label, longitudinal one-year study comparing *Lamictal* with lithium in 14 patients with rapid cycling bipolar disorder.[368] In the 7 patients receiving *Lamictal*, 6 (86%) had <4 mood episodes, 1 (14%) had >4 episodes, and 3 (43%) had no mood episodes in one year. In the 7 patients receiving lithium, 3 (43%) had <4 mood episodes and 4 (57%) had ≥4 episodes in one year. There was no evidence of preferential antidepressant versus antimanic efficacy.

Open-Label study as adjunctive therapy

Fatemi et al evaluated 5 patients (27-48 years of age) with rapid cycling, bipolar I or II disorder in an open-label study. [369] The mean dose and duration of therapy with *Lamictal* was 185 mg/day (range, 150-225 mg/day) and 225.8 days (range, 189-265 days), respectively. *Lamictal* was initially added to treatment with fluoxetine, methylphenidate, valproate, triiodothyronine, tetraiodothyronine, and lithium.

Four patients discontinued all psychiatric medications with exception of thyroid supplements and one patient received *Lamictal* with lithium and valproate. Improvement was demonstrated on all behavior scores after treatment with *Lamictal*; Beck Depression Inventory (BDI) symptoms and GAS scores both significantly improved over time ($P < 0.001$ and $P < 0.031$, respectively). It was calculated that every 100 mg of *Lamictal* administered resulted in a decrease of 4.1 symptoms using the BDI ($P < 0.30$) and a 10.5 point increase in GAS score ($P < 0.001$). There was a significant treatment by time effect for GAS scores ($P < 0.016$) with improvement of 5.59 points per 100 days with *Lamictal* versus 0.8 points per 100 days prior to *Lamictal*. One patient receiving *Lamictal* in combination with lithium and valproate experienced side effects including nausea, headache, dizziness, dry mouth, constipation, loose stools, rash, and tremor.

8.4 Use of *Lamictal* for Acute Treatment of Bipolar Depression in Adults

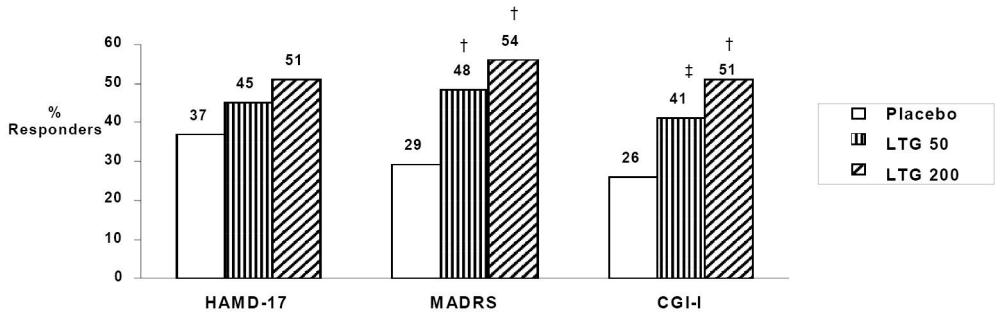
Placebo-controlled clinical trials

Acute Treatment of Bipolar I Depression (Study 1)

Calabrese et al evaluated the efficacy and safety of *Lamictal* as monotherapy for the treatment of acute bipolar I depression in a 7-week, multicenter, randomized, double-blind, parallel-group trial. [370] Patients (mean age, 40 years), moderately to markedly ill, were randomized to receive placebo (PBO, n = 66), or *Lamictal* 50 mg/d (n = 66) or 200 mg/d (n = 63). In both groups, *Lamictal* 25 mg/day was administered during weeks 1 and 2, and increased to 25 mg twice daily (BID) at week 3. Patients randomized to *Lamictal* 200 mg/day received 50 mg BID at week 4, and then 100 mg BID for weeks 5 through 7. Approximately two-thirds of patients had previously taken lithium (randomization was stratified according to lithium use).

Patients in the group receiving *Lamictal* 200 mg/d experienced significant improvement on all efficacy measures using both last observation carried forward (LOCF) and observed analyses, with the exception of the LOCF data from the Hamilton Rating Scale for Depression (HAMD)-17 (primary efficacy variable) and the observed and LOCF results of the HAMD-31 total score. Responder analyses are presented in Figure 28. The majority of patients (>90% in each group) were over 70% compliant with medication dosing during the trial.

Figure 28. Responder Analyses for Acute Bipolar Depression Study 1* (n = 192) [370]



*Response defined as ≥50% reduction on the 17-item HAM-D or MADRS scales or a rating of very much improved or much improved on the CGI-I scale. † $P < 0.05$ vs PBO, ‡ $P < 0.1$ (NS) vs PBO

A combined week 3 analysis (at which time both groups received *Lamictal* 50 mg/day) was conducted.[370] Patients receiving *Lamictal* demonstrated significant improvements by week 3 on the HAM-D depressed mood item (observed and LOCF), MADRS (observed), CGI-I (observed), and CGI for Severity (CGI-S) (observed).

There were no clinically significant changes in blood pressure, pulse, or weight in any treatment group. The frequency of adverse events were similar for patients receiving *Lamictal* 50 mg/d and 200 mg/d or PBO with the exception of headache (35% vs 32% vs 17%, respectively) ($P < 0.05$ vs PBO). Other common adverse events included nausea, pain, and dizziness. Rash was reported in 14%, 11%, and 11% of patients receiving *Lamictal* 50 mg/d, *Lamictal* 200 mg/d, and PBO, respectively. No cases of rash led to hospitalization or were considered serious. Rash led to discontinuation, from 4 to 31 days after initiation of treatment, in nine cases (PBO, n = 2; *Lamictal*, n = 7). Seven patients receiving *Lamictal* (5.4%) versus three receiving PBO (4.6%) developed manic, hypomanic, or mixed episodes, none of which required hospitalization. Six of the patients were receiving ≤50 mg/d of *Lamictal* and the episodes occurred during the first 3 weeks of treatment. One patient's episode occurred on day 24 while receiving *Lamictal* 100 mg/d.

Acute Treatment of Bipolar I Depression (Study 2)

Another 8-week, multicenter, double-blind, placebo-controlled, fixed-dose, trial evaluated the efficacy and safety of *Lamictal* as monotherapy for the treatment of acute bipolar depression.[371] Patients with bipolar I disorder were randomized to treatment with *Lamictal* (titrated to 200 mg/d, n = 133) or PBO (n = 124). *Lamictal* was initiated at 25 mg/d for weeks 1-2, 50 mg/d for weeks 3-4, 100 mg/d for week 5, and 200 mg/d for weeks 6-8. There was no statistically significant difference between *Lamictal* and PBO in mean change from baseline on MADRS scores (primary efficacy endpoint). Adverse events led to discontinuation in 12% of patients receiving *Lamictal* and 8% receiving PBO.[372] There were no differences between the groups in clinical laboratory values, body weight or vital signs. The incidence of mania was 3% for both *Lamictal* and PBO. Rash was reported in 9% of patients receiving *Lamictal* and 6% receiving PBO. There were no cases of serious rash and no deaths.

Acute Treatment of Bipolar I Depression (Study 3)

A similar multicenter, randomized, double-blind, placebo-controlled 8-week trial also evaluated the efficacy and safety of *Lamictal* as monotherapy (titrated to 200 mg/d, n = 131) compared with PBO (n = 128) in adults with bipolar I disorder for the acute treatment of a major depressive episode.[371] There was no statistically significant difference in the change in MADRS scores from baseline to week 8 between patients receiving *Lamictal* or PBO (primary endpoint). The most common (≥10%) adverse events for *Lamictal* and PBO, respectively, were headache (20% vs 21%), diarrhea (13% vs 6%), nausea (11% vs 10%), and dry mouth (10% vs 7%). Rash was reported by 6% of patients receiving *Lamictal* and 2% receiving PBO. There were no cases of serious rash or death. [373]

Acute Treatment of Bipolar I or II Depression

Adults with bipolar I or II disorder were evaluated in a multicenter, randomized, double-blind, placebo-controlled 10-week trial using *Lamictal* as monotherapy in the treatment of a major depressive episode.[371] Patients were randomized and stratified by primary diagnosis (bipolar I or II disorder) to

receive PBO (n = 103) or *Lamictal* (n = 103) gradually titrated to a flexible target dose of 100 to 400 mg/d. There were no statistically significant differences in change from baseline HAMD-17 scores between patients receiving *Lamictal* or PBO (primary efficacy endpoint).

In a post-hoc subgroup analysis (bipolar I and II), bipolar I patients receiving *Lamictal* showed greater improvements in observed values for HAMD-17 scores at day 64, MADRS scores at day 64 and 71, CGI-S scores at day 50 and 64, and CGI-I scores at day 64 as compared with PBO.[245] There was no significant difference in percent of responders (≥50% reduction on the HAMD-17 or MADRS scales or a rating of very much improved or much improved on the CGI-I scale) between patients receiving *Lamictal* or PBO. The efficacy analysis included 42 bipolar II patients each for *Lamictal* and PBO. On the HAMD-17, the percent of bipolar II patients who responded (45.2% (n = 19) for *Lamictal* and 47.6% (n = 20) for PBO) was similar between groups.

There were no clinically significant effects of *Lamictal* on weight, laboratory parameters or vital signs. The most common (≥10%) adverse events reported in either treatment group were headache, nausea, somnolence, dizziness, rash, infection, insomnia, pain, xerostomia, influenza, and diarrhea. The incidence of all rash was 17% for patients on *Lamictal* and 12% for patients on PBO. Rash led to discontinuation in six patients on *Lamictal* and two on PBO. No cases of rash led to hospitalization or were considered serious. The incidence of manic and hypomanic episodes was 7% (n = 7) and 4% (n = 4) for *Lamictal* and PBO, respectively.

Acute Treatment of Bipolar II Depression

Adults with bipolar II disorder were evaluated in a multicenter, randomized, double-blind, placebo-controlled 8-week trial using *Lamictal* as monotherapy in the treatment of a major depressive episode.[371] Patients were randomized to receive *Lamictal* (n = 111) gradually titrated to 200 mg/d or PBO (n = 110).

There were no statistically significant differences in change from baseline MADRS scores between patients receiving *Lamictal* (-13.4) or PBO (-12.0) (primary efficacy endpoint). CGI-I responder rate showed a significant treatment difference for *Lamictal* versus PBO ($P < 0.05$). The most common (≥10%) adverse events reported in either treatment group for *Lamictal* and PBO respectively were headache (28% vs 36%), diarrhea (7% vs 17%), and nausea (7% vs 14%). The incidence of all rash was 6% for both *Lamictal* and PBO. No cases of rash led to hospitalization or were considered serious. The incidence of mania-related events was 2% vs. 0% in patients receiving *Lamictal* and PBO, respectively.[374] There was no evidence of any clinically significant effects of *Lamictal* on weight, laboratory parameters or vital signs.

Acute Treatment of Bipolar Disorder and Major Depressive Disorder versus Gabapentin

Frye et al compared monotherapy with *Lamictal* (300-500 mg/d) or gabapentin (GBP, 4800 mg d) in 38 hospitalized patients with refractory mood disorders (including bipolar disorder and major depressive disorder) in a randomized, placebo-controlled, double-blind, cross-over trial.[375] Thirty-one patients (mean age, 39.2 years), including 11 diagnosed as bipolar I and 14 diagnosed as bipolar II, were evaluable for all three treatment phases. *Lamictal* was dosed 25 mg QD for week 1, 50 mg QD for week 2, 50-100 mg QD for week 3, 150-300 mg QD for weeks 4-5, and 300-500 QD for weeks 5-6 (faster than currently recommended).

Table 35. Response Rates* in Hospitalized Mood Disorder Patients Based on CGI-BP (primary endpoint)[375]

	Lamictal	**Gabapentin**	**Placebo**
Mania	11/25 (44%)	5/25 (20%)	8/25 (32%)
Depression	14/31 (45%)	8/31 (26%)	6/31 (19%)
Overall†	16/31 (52%)‡	8/31 (26%)§	7/31 (23%)
* Defined as much or very much improved; †Change from baseline (n = 31), $P = 0.031$; ‡ *Lamictal* vs GBP $P = 0.011$ and *Lamictal* vs PBO, $P = 0.022$; §GBP vs PBO, $P = 0.700$			

Mean daily doses at week 6 were *Lamictal* 274±128 mg and GBP 3987±856 mg. There was no difference in doses of either agent between responders and nonresponders. Response rates observed during the first phase of the trial (initial parallel group randomized component of this study) were similar to the whole

study; 50% (5/10) for *Lamictal*, 33% (3/9) for GBP, and 18% (2/11) for PBO.[375] When the response rates were analyzed as a function of a positive response in the preceding phase, only 23% of responders to *Lamictal*, 50% of GBP responders, and 0% of PBO responders were also partial responders in the previous phase and may have entered the next phase somewhat improved. Hamilton Rating Scale for Depression (HAM-D) scores, a secondary endpoint, for patients receiving *Lamictal* was also significantly reduced compared with patients receiving GBP ($P = 0.015$). A positive response to *Lamictal* was associated with fewer prior medication trials and hospitalizations, male gender, and bipolar diagnosis; while for GBP, response correlated with younger age, shorter duration of illness, and lower baseline weight. [376]

Commonly reported adverse events (≥10% in any group for *Lamictal*, GBP, and PBO, respectively) were ataxia (3%, 10%, 0%), diarrhea (6%, 6%, 13%), diplopia (0%, 10%, 3%), fatigue (0%, 10%, 3%), and headache (3%, 13%, 13%).[375] One patient receiving *Lamictal* developed rash during week 15 of continuation treatment which progressed to toxic epidermal necrolysis and required burn-unit hospitalization; the patient fully recovered. There was statistically significant weight change among patients receiving GBP compared with *Lamictal* (+1.83±5.04 kg vs -0.96±3.11 kg, $P = 0.021$).

8.5 Use of *Lamictal* for Acute Treatment of Manic and Mixed Episodes in Adults with Bipolar Disorder

Randomized Study in dysphoric mania versus Gabapentin and Carbamazepine

Mokhber et al compared the effectiveness of *Lamictal* (100 mg/d), gabapentin (GBP, 900 mg/d), and carbamazepine (CBZ, 600 mg/d) in a single-center, double-blind, randomized study of 59 adult outpatients with DSM-IV criteria for dysphoric mania (depressive features in mania).[377] The primary endpoint was the change in total scores of the Minnesota Multiphasic Personality Inventory from baseline to week 8. There were significant improvements in symptoms of mania across all 3 treatment groups in depression and mania subscales ($P < 0.05$). GBP demonstrated significant improvement over CBZ on the hypomania subscale ($P = 0.046$). Improvement in psychomotor acceleration was higher in patients receiving GBP and compared to CBZ ($P = 0.003$). The total depression score significantly improved across all 3 treatment groups, and was significantly higher in patients receiving GBP compared to *Lamictal* and higher in *Lamictal* and GBP compared to CBZ ($P < 0.05$). In the subdimensions of depression, there was no significant difference between groups on the subjective score ($P > 0.05$), but there were significant improvement in psychomotor retardation and body dysfunction with *Lamictal* and GBP compared to CBZ ($P < 0.05$). Greater improvements in mental dullness and brooding were noted with GBP compared to *Lamictal* or CBZ ($P < 0.01$). Eight patients withdrew from the study secondary to adverse events: 6 patients taking CBZ due to GI upset and/or vertigo and 2 patents taking GBP due to severe drowsiness and/or skin itching.

8.6 Use of *Lamictal* for the Treatment of Bipolar II Disorder in Adults

Suppes et al conducted a 16-week, open-label study comparing *Lamictal* and lithium as monotherapy for the treatment of acute depression in 102 patients (mean age, 36.4 years) with bipolar II disorder, of which 76% were rapid cyclers based on DSM-IV criteria.[378] Patients were titrated to 200 mg/day of *Lamictal* (n = 44) over 8 weeks or ≥ 900 mg/day of lithium (n = 54) over 2 weeks (maximum serum level 1.2 mEq/L). Mean scores (± standard deviation) on the HAM-D_{17} decreased from 20.8 ± 4.27 at baseline to 8.00 ± 1.28 at 16 weeks in patients who took *Lamictal*, and from 21.2 ± 4.15 to 6.97 ± 1.33 in patients who took lithium (primary endpoint; $P < 0.0001$ for both). The between-group difference was not significant. The subset of patients with a history of rapid cycling demonstrated significant improvement on the HAM-D_{17} at 16 weeks in both treatment groups ($P < 0.001$), with no significant differences between groups. Both treatment groups demonstrated significant baseline to endpoint inprovement on the Montgomery-Asberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), the Clinical Global Impression Scale for Bipolar Disorder (CGI-BP), and the Global Assessment of Functioning (GAF) ($P < 0.001$ for all). Between-group differences were not significant on these scales . The subset of patients with a history of rapid cycling demonstrated significant improvement on the MADRS, YMRS, CGI-BP, and GAF at 16 weeks in both treatment groups ($P < 0.001$ for all), with no significant differences between groups. Fifty-six percent of patients terminated the study early. The mean number (±SD) of side effects reported by patients who received *Lamictal* was 4.2 (± 3.2) and the mean number of side effects reported by patients who received lithium was 9.2 (± 6.4) ($P<0.001$). The most frequent side effects in patients who

received *Lamictal* were nausea/vomiting (24.4%), upset stomach (19.5%), dry mouth (19.5%), tremors (9.8%), and drowsiness/panic (9.8%).

Herman et al described the efficacy and tolerability of treatment with *Lamictal* (100 mg/d) in an open-label study of 22 adult patients (17 female, 5 males; 15 rapid-cycling, 7 non-rapid-cycling) with bipolar II disorder. [379,380] Mean patient age was 26.5 years (range, 20 – 44). The mean number of depressive and hypomanic episodes was compared for the 6 months before and after treatment with *Lamictal*. Breakthrough depressive episodes were temporarily treated with paroxetine and breakthrough hypomanic episodes were temporarily treated with risperidone. The mean number of hypomanic (0.91 vs. 0.36, $P < 0.001$) and depressive (1.73 vs. 0.46, $P < 0.001$) episodes decreased during 6 months of treatment with *Lamictal*. Average length of episodes (days) also decreased after 6 months of treatment: depressive (31.1 vs. 19.4, $P < 0.001$) and hypomanic (9.2 vs. 8.1 , $P < 0.001$). Rapid-cycling patients gained an average of 7.2 days free from depressive symptoms and non-rapid-cycling patients gained an average of 21.9 days. Rapid-cycling patients gained an average of 1.5 days free of hypomanic symptoms, non-rapid-cycling patients gained an average of 7.0 days. Non-rapid-cycling patients reported no hypomanic symptoms days after 6 months of monotherapy with *Lamictal*. Global functioning as evaluated by the Global Assessment of Functioning (GAF) scale also improved with treatment. *Lamictal* was considered well tolerated with no serious adverse events.

Vieta et al assessed the efficacy of *Lamictal* by measuring HAM-D, Young Mania Rating Scale (YMRS), and CGI-BP over a 6 month period in an open-label study of 17 patients with bipolar II disorder. [381] Patients had previously poor responses to lithium or other mood stabilizers. Three patients discontinued the study (n = 1 vomiting, n = 2 mild rash). The mean dose of *Lamictal* was 202±64.4 mg/d. The 12 patients who completed the study had significant improvement in HAM-D ($P = 0.004$), and the depressive and overall subscales of the CGI-BP (both $P = 0.002$).

8.7 Use of *Lamictal* in Children and Adolescents with Bipolar Disorder

Open-Label Studies

Chang et al evaluated the safety and efficacy of *Lamictal* as adjunctive or monotherapy in an 8-week, prospective, open-label study in 20 adolescents (ages 12-17 years, mean 15.8 years) with bipolar I (n=7) or II (n=6) disorder or NOS (n=6) experiencing a depressive episode. Comorbidities included attention-deficit hyperactivity disorder (n=13), anxiety disorder (n=10), oppositional defiant disorder (n=9), and psychosis (n=3).[382]

The primary measure for response was “very much improved” (1) or “much improved” (2) on the Clinical Global Impression-Improvement (CGI-I) at week 8. A secondary measure for positive response was defined as ≥50% decrease in Children’s Depression Rating Scale-Revised (CDRS-R) score from baseline to week 8. *Lamictal* was added to current stable regimens of medications or psychotherapy (if any), initiated at 12.5-25 mg/d, and increased by 12.5-25 mg every 1-2 weeks to reach a target dose of 100-200 mg/d.

The mean dose of *Lamictal* at week 8 was 131.6 mg/d. Seven patients were taking concomitant psychotropic medications (including lithium, VPA, olanzapine, methylphenidate, alprazolam, trazodone, atomoxetine, and aripiprazole) with *Lamictal*. Of the 19 evaluable patients, 16 (84%) responded to treatment with *Lamictal* (CGI-I of 1 or 2) and 12 (63%) experienced ≥50% decrease in the CDRS-R. CDRS-R scores at week 8 were different between responders and non-responders ($P = 0.01$). Gender, age, type of bipolar disorder, presence of comorbid conditions, baseline CDRS scores, and monotherapy versus adjunctive did not predict response. Remission (CDRS-R ≤28 and CGI-S of 1 or 2) was achieved in 58% of patients following treatment with *Lamictal*. Mean scores at baseline and week 8 are presented in Table 36.

Table 36. Mean Baseline and Week 8 Assessments of Efficacy in Chang et al Study (n = 19)[382]

Efficacy Measure	Baseline: number (± SD)	Week 8: number ± (SD)
CDRS-R	58 (12.7)	28 (11.6)*
YMRS	16.6 (8.6)	9.8 (8.1)*
OAS-Aggression	48.9 (50.2)	16.7 (24.7)*
OAS-Irritability	6.4 (1.6)	3.3 (2.5)*
OAS-Suicide	1.56 (2.1)	0.26 (0.65)*
* $P < 0.05$ versus baseline; CDRS-R (Children’s Depression Scale-Revised); YMRS (Young Mania Rating Scale); OAS (Overt Aggression Scale – Modified)		

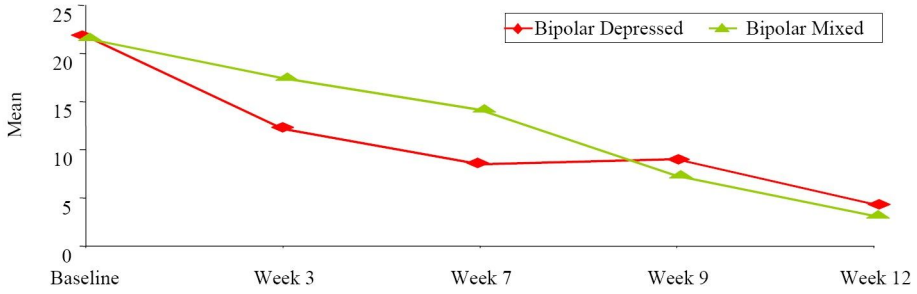
Patients did not experience weight change from baseline ($P = 0.34$), rash, laboratory abnormalities, exacerbation of mania, or other serious adverse effects during the study.[382] One patient withdrew during week 2 due to chronic suicidal ideation and was not included in the final analysis. The most common adverse events included headache (84%), fatigue (58%), nausea (53%), sweating (47%), and difficulty sleeping (10.5%).

Swope et al evaluated the safety and efficacy of *Lamictal* as monotherapy in a single-center, outpatient, 12-week, open-label study in adolescents (ages 13–17 years, mean 15 years) diagnosed with bipolar I disorder, depressed (n=6) or mixed phase (n=7).[383] Five patients were previously treated for mood disorders, with such medications as bupropion, selective serotonin reuptake inhibitors, atypical antipsychotics, and stimulants. Changes in the Montgomery-Asberg Depression Rating Scale (MADRS) and Hamilton Rating Scale for Depression (HAM-D) score from baseline to end of treatment were primary efficacy measures.

Lamictal was initiated and titrated according to the following schedule: 25 mg/d for weeks 1 and 2, 50 mg/d for weeks 3 and 4, 100 mg/d for week 5, 200 mg/d for week 6, and increased up to a maximum dose of 400 mg/d if needed based on CGI evaluation scores (week 8). Patients taking ≥50 mg/d of *Lamictal* underwent a taper period beginning at week 12 in which the current dose was reduced by half each week until completely discontinued. Concomitant use of other psychotropic drugs was prohibited with the exception of lorazepam (up to 1 mg/d) short-term.

Mean scores decreased from baseline to week 12 on MADRS (21 to 4, Figure 1), CGI-S (4 to 1), CDRS-R (73 to 40) and Young Mania Rating Scale (YMRS, 20 to 6). Preliminary data did not include HAM-D scores. The mean dose of *Lamictal* was 241 mg/d at week 12. See Figure 29.

Figure 29. Montgomery-Asberg Depression Rating Scale at Baseline through Week 12 (n = 13)[383]



Of 23 patients enrolled, 13 completed the study.[383] Three patients withdrew early due to non-compliance, five were lost to follow-up, and two discontinued for suicidal ideation requiring hospitalization. No patients discontinued due to adverse events related to *Lamictal*.

Pavuluri et al prospectively evaluated the effects of *Lamictal* as monotherapy on the neurocognitive profile of pediatric patients with bipolar disorder.[266] Please note that *Lamictal* is not approved for use in patients <18 years of age with bipolar disorder. They studied 65 subjects (mean age, 13 years) including 32 patients with bipolar I or II disorder, index manic, hypomanic, or mixed episodes; and 33 healthy controls matched on age, sex, race, socioeconomic status, IQ and reading ability. All subjects completed tests on attention, executive function, attention, verbal learning, working memory and emotion recognition before and after the 16-week study period. The dose of *Lamictal* was escalated for 8 weeks and maintained for 8 weeks. Rescue treatment with atypical antipsychotics was allowed only during the escalation phase. According to preliminary data, the final mean dose of *Lamictal* was 212 mg/day. There was no evidence of deterioration in any neurocognitive domain after treatment with *Lamictal*. Working memory deficits present at baseline in patients were significantly improved following treatment relative to changes in healthy controls. Facial emotion recognition improved after treatment, especially for happy child faces relative to angry and adult facial emotions. Attention domain deficits did not significantly improve. On clinical outcome measures,

patients significantly improved from baseline to end of treatment on the Young Mania Rating Scale (21.74 vs 5.35, $P < 0.001$) and on the Child Depression Rating Scale (51.5 vs 24.7, $P < 0.001$).

Retrospective Reviews

Ginsberg et al conducted a chart review of 92 children and adolescents (aged 7-17 years, mean 15 years) with bipolar disorder to assess safety and efficacy of *Lamictal* in a private practice setting.[384] Distribution of diagnoses were bipolar I disorder in 26.1%, bipolar II disorder in 42.4%, and bipolar disorder NOS in 31.5%. Response was defined as CGI-I scores of 1 or 2. Relapse was defined as a mood change occurring 4 weeks after initiation of medication or the return of symptoms from the original mood episode. The mean final dose of *Lamictal* was 100.5 mg/d. Approximately half of patients (n = 55, 59.8%) had marked to moderate improvement (CGI-I of 1 in 16.3% and 2 in 43.5%), 77 (83.7%) responded and nearly one-third (n = 32, 34.8%) relapsed (mean time = 143 days) during treatment with *Lamictal*. Non-serious rash (14.1%) and headache (5.4%) were the most frequently reported adverse events.

Herrmann et al performed a chart review of 66 patients (≤18 years) receiving *Lamictal* for the treatment of bipolar disorder to assess efficacy and tolerability.[385] Twenty-eight patients (6 females, 22 males) were within the pediatric range of 4-11 years (mean age, 9 years) and 38 (12 females, 26 males) were within the adolescent age range of 12-17 (mean age, 15 years). Diagnoses were bipolar I disorder in 54%, bipolar II disorder in 7%, and bipolar disorder NOS in 39%. There was a high rate of comorbid psychiatric diagnoses (79% pediatric, 89% adolescent) and family history of psychiatric disorders (89% pediatric, 87% adolescent). The primary outcome measure was the CGI score at 12 months after initiation of *Lamictal*. The mean dose of *Lamictal* was 25 mg/d at baseline and 300 mg/d at 12 months. More than one-third of patients (37% overall; 39% pediatric, 36% adolescent) showed at least a moderate improvement on the CGI with no significant adverse events. Four patients (3 pediatric and 1 adolescent) discontinued *Lamictal* due to adverse events (rash n = 3, nausea n = 1).

Swope et al retrospectively assessed the long-term safety and efficacy of *Lamictal* in the treatment of 30 adolescents (ages 13-17 years, mean age 15.6 years) with a primary diagnosis of bipolar disorder.[386] Most patients were females (n = 25) with bipolar disorder, NOS (n = 17) and had a family history of mental illness (n = 24). Over half of the patients had previously been treated with a benzodiazepine or antidepressant (n = 17). Most patients received *Lamictal* upon initial diagnosis of bipolar disorder (n = 24). The average dose of *Lamictal* at months 8 and 12 were 132 mg and 108 mg (range 25-200 mg), respectively. At baseline, half of the patients (n = 15) had severe and the other half (n = 15) experienced moderate symptoms. Following 12 months of treatment with *Lamictal*, no patients (0%) had severe symptoms, two (40%) had moderate symptoms, and 3 (60%) had mild symptoms. Overall, five of 30 patients received *Lamictal* for >12 months and were consistently euthymic. Adverse events included suicidal ideation (n = 2), urinary frequency (n = 2), difficulty sleeping (n = 1), dizziness (n = 1), non-pruritic rash (n = 1), sleepiness (n = 1). One patient discontinued treatment due to a rash that resolved without sequlae.

Carandang et al retrospectively evaluated 42 adolescents (mean age 16 years) with bipolar disorder or refractory depression (n = 21 bipolar depression, n = 12 unipolar depression, n = 9 mood disorder NOS) treated with *Lamictal* as monotherapy (n = 6) or as add-on therapy (n = 36).[387] Concurrent psychotropics included: antidepressants (n = 15), antipsychotics (n = 22), mood stabilizer (n = 7), stimulants (n = 12), and anxiolytics (n = 3). The mean daily dose of *Lamictal* was 115 mg/day (range, 10-300 mg/day) and mean duration of treatment was 29 weeks. Mean Clinical Global Impression – Severity (CGI-S) scores significantly decreased from baseline to endpoint [4.9±1.0 (markedly ill) to 3.5±1.4 (mildly ill); $P < 0.002$]. Improvement, defined as CGI-Improvement score of 1 (very much improved) or 2 (much improved) was observed in 52% of adolescents. Four patients experienced benign rash, which resolved after discontinuation of *Lamictal*. One patient experienced severe, generalized pruritis, after abrupt discontinuation of an oral contraceptive (OC); the pruritis resolved after reinitiation of the OC. Sedation led to discontinuation in 2 patients.

Mandoki retrospectively studied the effectiveness of *Lamictal* in combination with VPA in the treatment of refractory pediatric patients with bipolar disorder.[388] The medical records of 10 children and adolescents (ages not provided) were evaluated. Dosages ranged from 50-200 mg/d for *Lamictal* and 500-1500 mg/d for VPA. Efficacy, measured by the CGI Scale, showed improvement when *Lamictal* was added to VPA. Rash was not reported.

Salpekar et al retrospectively evaluated 38 pediatric patients (mean age 10.4 years, range 6-17 years) with seizure disorders and comorbid bipolar sepctrum disorders receiving 11 different AEDs, including *Lamictal* (n = 6).[389] Commonly reported mood disorder symptoms included impulsivity (n = 37), psychomotor agitation (n = 37), sudden affective outbursts (n = 30), distractibility (n = 29), and explosive rage (n = 28). Clinical improvement was defined as CGI-I ratings of 1-2. In the 22 patients who received *Lamictal*, VPA, carbamazepine, or oxcarbazepine as monotherapy, CGI ratings were better than the 8 patients receiving other agents as monotherapy ($P = 0.003$). Use of *Lamictal*, as monotherapy or adjunctive therapy, was associated with significant improvements ($P = 0.007$) in bipolar spectrum symptoms.

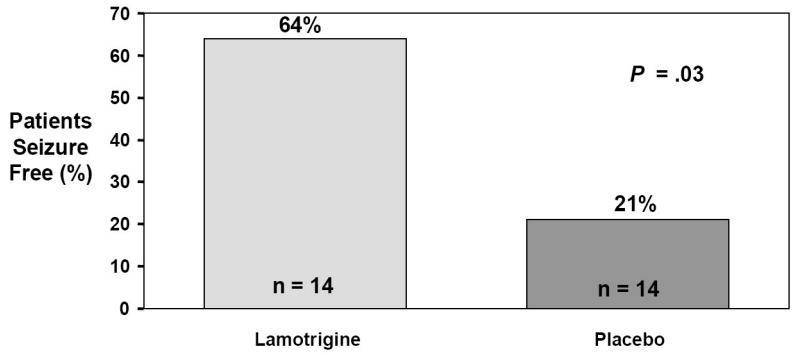
8.8 Use of *Lamictal* in the Treatment of Absence Seizures

absence seizures: clinical studies

Frank et al evaluated the efficacy and tolerability of monotherapy with *Lamictal Tablets* in 45 children with newly diagnosed typical absence seizures. [333] The study, using a "responder-enriched" design, began with an open-label phase and was followed by a double-blind, placebo (PBO)-controlled phase. Patients (aged 2-16 years) initiated *Lamictal Tablets* 0.5 mg/kg/day (d) for two weeks followed by 1 mg/kg/d for two weeks. Doses of *Lamictal Tablets* were then increased by 1 mg/kg/d weekly until the patient became seizure-free during hyperventilation testing with electroencephalogram (EEG) recording or reached the maximum allowable dose of *Lamictal Tablets* (15 mg/kg/d). The maximum allowable dose was increased from 7 mg/kg/d to 15 mg/kg/d or an absolute limit of 1000 mg/d after 20 patients had been treated and some patients were not seizure-free, as required by the study design. Responders were then randomized to *Lamictal Tablets* (at the effective dose determined during the open-label portion, median = 5 mg/kg/d) or PBO for four weeks or until seizures, confirmed by hyperventilation testing with EEG, occurred.

Thirty of 42 patients (71%) who completed the dose escalation phase became seizure-free at a median dose of 5 mg/kg/d (range, 2–15 mg/kg/d). Eighteen of the 22 patients (82%) whose maximum allowable dose was 15 mg/kg/d became seizure-free. Twenty-eight patients entered the double-blind phase, 14 on *Lamictal Tablets* and 14 on PBO. Intent-to-treat analysis results are shown in Figure 25Figure 30.

Figure 25. Intent-to-Treat Analysis of Seizure-Free Rates in Children with Absence Seizures [333] Figure 30. Intent-to-Treat Analysis of Seizure-Free Rates in Children with Absence Seizures [333]



Drug-related adverse events reported in ≥5% of patients included abdominal pain (n = 5), headache (n = 2), nausea (n = 3), anorexia (n = 2), dizziness (n = 3), and hyperkinesia (n = 2). [333] Ten patients experienced rashes with only one case considered attributable to *Lamictal Tablets*. No patients were withdrawn due to adverse events. There were no signs of consistent changes in weight, vital signs, or clinical laboratory values.

Beran et al conducted a multicenter, double-blind, placebo-controlled, crossover trial of adjunctive therapy with *Lamictal* in 26 patients (ages, 15-50 years) with treatment-resistant generalized epilepsy.[204] Seizure types included absence and tonic-clonic (n = 12); absence alone (n = 8); and absence, myoclonic, and tonic-clonic (n = 2). All patients received valproate (VPA; mean daily dose 2750 mg) either as monotherapy (n = 11) or in combination with other AEDs. The trial consisted of two 8-week treatment periods followed by a 4-week washout period. *Lamictal*, dosed 150 mg/d in patients taking VPA with an

enzyme-inducing antiepileptic drug (EIAED) and 75 mg/d in patients taking VPA without an EIAED, or placebo (PBO) was added to the patient's existing regimens of ≤4 AEDs. The dose escalation was faster than currently recommended. Open-label continuation treatment was offered at the end of the trial.

Twenty-two patients completed the trial. There was a significant reduction in frequency of tonic-clonic seizures and absence seizures following treatment with *Lamictal* versus PBO ($P = 0.03$ and $P < 0.001$, respectively). Overall, a ≥50% seizure reduction was observed for tonic-clonic seizures in 50% of patients and for absence seizures in 33% of patients compared with PBO. Plasma concentrations of lamotrigine were 1.3-5.2 mg/L. Rash was the only adverse event leading to discontinuation of *Lamictal* (n = 2). Most adverse events were rated as mild to moderate. Adverse events reported in >5% during treatment with *Lamictal* and greater than PBO were rash (n = 7), ataxia (n = 3), diplopia (n = 3), dizziness (n = 2), tremor (n = 2), and drowsiness (n = 2); tiredness was reported in five patients receiving PBO versus one receiving *Lamictal*. The majority of patients (n = 23) choose to continue open-label *Lamictal*, with 20 receiving *Lamictal* for a mean of 26 months. In these 20 patients, 80% had ≥50% seizure reduction and 25% (n = 5) were seizure-free.

Coppola et al prospectively compared *Lamictal* (n = 19) and valproate (VPA; n = 19) as monotherapy in 38 newly diagnosed children and adolescents (aged 3-13 years; mean 7.5 years) with typical absence seizures.[390] After undergoing awake video-electroencephalogram (EEG) recordings with hyperventilation and intermittent photic stimulation, patients were randomized to *Lamictal* or VPA and followed for up to 12 months. *Lamictal* was initiated at 0.5 mg/kg/day for 2 weeks (twice daily) and increased to 1.0 mg/kg/day for 2 additional weeks. Doses were increased by 1.0 mg/kg/day every 5 days until seizure control was achieved, intolerable adverse events occurred, or a maximum of 12 mg/kg/day was reached (last follow-up: mean dose 8.3 mg/kg/day, serum drug level 8.1 mg/L). VPA was initiated at 10 mg/kg/day, and increased every 3 days by 5 mg/kg/day until seizures were controlled, intolerable adverse events occurred, or a maximum of 30 mg/kg/day was reached (last follow-up: mean dose 25.4 mg/kg/day, serum drug level 76.8 mg/L). At 1 month, 5.3% and 52.6% of patients were seizure free while taking *Lamictal* and VPA, respectively ($P = 0.004$). At 3 months, these rates were 36.8% and 63.1% for *Lamictal* and VPA, respectively (P = NS) and at 12 months, 52.6% and 68.4% (P = NS). Adverse events reported in patients taking *Lamictal* included headache (n = 2), transient mild rash (n = 1), diplopia (n = 1), nervousness (n = 1), and increased appetite (n = 1). Adverse events in patients taking VPA included diarrhea (n = 1) and weight gain (n = 1). No patients withdrew secondary to adverse events.

Coppola et al prospectively evaluated the efficacy, tolerability, and effect on interictal generalized epileptiform discharges of *Lamictal* as monotherapy in 20 consecutive newly diagnosed children and adolescents (aged 3-10 years; mean 6.9 years) with typical absence seizures. [391] Ambulatory (24 hour) EEG monitoring was conducted at baseline and during maintenance. In the first two weeks, *Lamictal* was dosed at 0.5 mg/kg/day then increased to 1.0 mg/kg/day for an additional two weeks. Thereafter, based on clinical response, the dose was increased by 1 mg/kg/day (mean daily dose: 6.2 mg/kg, range 1.2-11 mg/kg). After a mean follow-up of 10.8 months, 55% (n = 11) of patients were 100% seizure free, 20% (n = 4) achieved >75% seizure reduction, and 25% (n = 5) achieved >50% seizure reduction. After a mean of 4-6 months, *Lamictal* significantly decreased the total number of interictal generalized spike-wave discharges per day($P = 0.0018$). Adverse events occurred in 3 patients and included hyperkinesias (n = 3), aggressiveness (n = 2), sleep disturbance (n = 2), increased appetite (n = 1), transient itchiness (n = 1), headache (n = 1). These resulted in drug withdrawal. Three patients experienced a mild, macular rash which resolved spontaneously after a few days (possibly related to alternative causes).

Buoni et al prospectively evaluated *Lamictal* in 15 children and adolescents (aged 3-13 years) with typical absence seizures.[392] *Lamictal* was administered as adjunctive therapy to 8 patients with absence seizures resistant to VPA or ethosuximide and to 7 patients as monotherapy with untreated absence seizures. In patients taking concomitant VPA, *Lamictal* was initiated at 0.2 mg/kg/day (final median daily dose, 2.9 mg/kg). In previously untreated patients, *Lamictal* was started at a dose of 0.5 mg/kg/day (final median daily dose, 6.9 mg/kg). Treatment-resistant patients achieved complete seizure control with adjunctive *Lamictal* after an average of 19 days. In the monotherapy group, complete seizure control was achieved after 40 days. In 5 treatment-resistant patients, VPA was withdrawn after a mean of 12.5 months, and *Lamictal* monotherapy was continued. This resulted in one patient experiencing relapses after 1 month, and VPA was reinitiated with full control achieved. EEGs normalized in all treatment-resistant patients after a median of 3 months with combination therapy. EEGs normalized in 5 of 7 patients taking

initial monotherapy with *Lamictal* after a median of 2 months. One patient taking initial monotherapy experienced a rash on the hands, face, and trunk. *Lamictal* was discontinued and the rash resolved in 6 days.

Lerman-Sagie and Lerman prospectively evaluated the efficacy of *Lamictal* as adjunctive therapy to antiepileptic drug (AED) regimens including VPA in 10 adult patients (aged 23 - 44 years) with intractable absence and generalized tonic-clonic (GTC) seizures. [393] Three patients had recurrent absence status. Patients were followed from 1 to 4 years. *Lamictal* was added to VPA at an initial dose of 0.2 mg/kg/day (administered twice daily), and increased to a maximum of 5 mg/kg/day, based on clinical response. Final doses of *Lamictal* were 200 to 300 mg/day. Most other AEDs, except VPA, were gradually discontinued. GTC seizures ceased completely in all patients. Absence seizures ceased completely in 7 patients, while 3 patients had >75% reduction in seizure frequency. Absence status did not recur after *Lamictal* was added. One patient experienced an increase of previous paranoid symptoms, but *Lamictal* was not discontinued. No other adverse events were reported.

8.9 Use of *Lamictal* for the Treatment of Juvenile Myoclonic Epilepsy

placebo-controlled study of lamictal as adjunctive therapy

Trevathan et al evaluated the efficacy and tolerability of *Lamictal* as adjunctive therapy in a subset of patients (ages 2-52 years) with JME and PGTC seizures.[6,394] Of 117 patients enrolled in a randomized, double-blind, placebo-controlled trial of *Lamictal* as adjunctive therapy for PGTC seizures, 33 patients also had diagnostic characteristics of JME and were included in the sub-analysis [*Lamictal* (n = 17) versus placebo (n = 16)]. The study phases included screening (≤2 weeks), baseline (8 weeks), titration (7 or 12 weeks depending on patient's age), and maintenance (12 weeks). *Lamictal* was administered at fixed doses targeting 200-400 mg/d and 3-12 mg/kg/d based on patient age and concomitant AED. The median percent decrease from baseline in PGTC seizures (primary efficacy endpoint) during the entire treatment period was 72% and 16% in the patients receiving *Lamictal* and placebo, respectively ($P = 0.020$). For all generalized seizure types, the median percent change from baseline in seizure frequency was a 44% decrease and 20% increase in patients receiving *Lamictal* and placebo, respectively ($P = 0.011$). No patients reported increased frequency or intensity of myoclonus. Two patients receiving *Lamictal* (n = 1 intentional carbamazepine overdose, n = 1 status epilepticus) and none receiving placebo discontinued due to an adverse event. The most common adverse events (≥10%) for *Lamictal* and placebo, respectively, were headache (12% and 25%), somnolence (12% and 6%), insomnia (12% and 0%), ear pain (0% and 13%), and decreased appetite (0% and 13%).

open-label studies

A multicenter, open-label study evaluated the efficacy and tolerability of monotherapy with *Lamictal Tablets* in patients ≥12 years with JME who were newly diagnosed or were receiving valproate (VPA) with inadequate seizure control or unacceptable side effects. [335] [336] The study consisted of 3 phases: 1) a 2-week screening; 2) an 8-week dose escalation during which *Lamictal Tablets* was titrated up to 100-500 mg/d, per Prescribing Information and clinical response while VPA was tapered; and 3) a 24-week treatment phase during which the dose of *Lamictal Tablets* could be adjusted to achieve optimal clinical benefit.

On average, patients previously treated with VPA (n = 63) were 29 years old (range 12-50 years) and had six days per month with myoclonic seizures. During the treatment phase (n = 51), the mean dose of *Lamictal Tablets* was 314 mg/d. The majority (86%) of patients completing the study experienced no deterioration in myoclonic seizure control when switching from VPA to *Lamictal Tablets*. Most patients (63%) rated their satisfaction with *Lamictal Tablets* as monotherapy as "much better" than VPA. Approximately half (52%) of patients experienced a ≥50% reduction in days with myoclonic seizures versus baseline and 50% and 82% of patients in generalized tonic-clonic (GTC) seizures and absence seizures, respectively. At the end of the treatment phase, investigators perceived that 67% of completers showed mild, moderate, or marked improvement in global clinical status and 50% of patients had improved adverse events from baseline. The most commonly (≥10%) reported drug-related adverse events were headache (21%), dizziness (21%), tremor (11%), and rash (10%).

In the newly diagnosed patients (n = 29; mean age, 24 years [range, 12-50 years]), the mean dose of *Lamictal Tablets* was 317 mg/d (range, 100-500 mg/d). During the treatment phase, 58% of patients experienced a ≥50% reduction in days with myoclonic seizures versus baseline, and 56% and 38% of

patients in the frequency of generalized tonic-clonic seizures and absence seizures, respectively. Two patients (7%) experienced an increase of >25% in myoclonus from baseline. At the end of the treatment phase, investigators perceived that 72% of patients showed mild, moderate, or marked improvement in global clinical status from baseline. The most commonly (≥10%) reported adverse events considered possibly drug-related were dizziness (17%), headache (14%), and somnolence (10%).

Fallah et al studied 24 patients with JME who failed therapy (37%) or experienced significant drug reactions while receiving VPA, ethosuximide, benzodiazepines, and piracetam. [395] Patients were given *Lamictal* (final dose of 200-400 mg/d) and compared to a 3-month baseline period; global assessment of seizure control was 88% with no serious adverse events.

retrospective reviews

Prasad et al retrospectively compared the efficacy and tolerability of *Lamictal*, topiramate (TPM), and VPA as monotherapy or polytherapy to the efficacy and tolerability to phenytoin (PHY) and carbamazepine (CBZ) in 72 patients (ages, 21-55 years) with JME. [396] Thirty-seven (51%) of patients received monotherapy throughout the entire treatment period, while 35 (49%) received polytherapy. Seizure outcome did not differ amongst patients receiving monotherapy with VPA (n = 36) versus *Lamictal* (n = 14) or between patients receiving polytherapy with VPA (n = 22) versus *Lamictal* (n = 21) or TPM (n = 15) ($P > 0.05$ for all). VPA, *Lamictal*, and TPM did not differ significantly in control of GTC, myoclonic or absence seizures. In evaluation of combined data of all 3 AEDs; control of myoclonic seizures was worse versus of GTC seizure control ($P = 0.03$), but not when compared with absence seizure control ($P = 0.43$). VPA, *Lamictal*, and TPM, when compared with PHY or CBZ, demonstrated better control of myoclonic seizures ($P < 0.01$ for all), but not GTC seizures ($P < 0.01$ for all). The withdrawal rate (per patient-year of treatment) of VPA was lower compared with the rates of TPM ($P = 0.003$), PHY ($P = 0.02$), and CBZ ($P = 0.001$), but not with *Lamictal (*$P = 0.12$). Approximately half of the withdrawals from *Lamictal*, VPA, and TPM were due to lack of seizure control or adverse events.

Martinez and Fountain retrospectively examined the response to *Lamictal* in 22 patients (mean age 32.5 years) with JME to determine relative worsening or improvement of myoclonic and other seizure types.[397] Of the 65 identified patients with JME, 22 were taking *Lamictal*; 15 had follow-up at 3 and 6 months, and 11 patients had follow-up for ≥12 months. Seizure reduction (≥50%) occurred at 3, 6, and 12 months in 9 (72%), 11 (100%, $P < 0.05$), and 11 (100%, $P < 0.05$) for GTC, respectively; and in 6 (40%), 11 (73.3%), and 6 (54.5%) for myoclonic seizures, respectively. At 12 months, all patients with GTC, 6 (54%) with myoclonic seizures, and both patients with absence seizures became seizure-free. Two patients experienced myoclonic exacerbation during the first 3 months, but this subsided in <12 months, and both became seizure-free at 12 months. One patient (5%) reported myoclonic exacerbation 9 months after initiating *Lamictal* that led to discontinuation.

Welty et al conducted a retrospective review of 36 patients (≥15 years) diagnosed with JME initiated on *Lamictal*, TPM, zonisamide (ZNS), and levetiracetam (LEV).[398] Results are presented in Table 37. Rates of adverse events were similar before and after starting a new AED.

Table 37. Change in Seizure Frequency and VPA Dosing in Patients with JME [398]

	***Lamictal* (n = 22)**	**Topiramate (n = 6)**	**Levetirac-etam (n = 4)**	**Zonisamide (n = 4)**
Change in myoclonic seizures	↑ 13%	↓ 34%	↑ 20%	↓ 10%
Change in generalized tonic-clonic seizures	↑ 140%	↓ 94%	↑ 397%	↓ 78%
Change in absence seizures*	↓	↓	↑	↓
Change in VPA doses	↓ 56%	↓ 53%	↑ 14%	↓ 37%
Able to discontinue VPA	36%	50%	25%	50%
*percents not provided; ↔ = unchanged, ↑ = increase, ↓ = decrease				

Carrazana et al retrospectively evaluated 24 patients (15-53 years) with JME receiving *Lamictal* (mean dose of 310 mg/d [range, 150-600 mg/d]).[399] Of the 24 patients, 21 were seizure-free (85.5%) and 2 (8.33%) developed dramatic exacerbation of their myoclonus leading to discontinuation of *Lamictal*. An additional two patients had a mild increase in morning myoclonus, but it was tolerable and transient. Reported adverse events included anxiety (n = 4), mild transient rash (n = 2, managed by dose reduction), and dizziness (n = 1).

8.10 Use of *Lamictal* for the Treatment of Refractory Major Depressive Disorder

Controlled monotherapy trials

Lamictal as monotherapy in the treatment of adult outpatients (mean age, 38 years) with MDD was studied in an 8-week, multicenter, randomized, double-blind, fixed-dose trial comparing *Lamictal* 200 mg/d (n = 152), desipramine 200 mg/d (DSP, n = 151), and PBO (n = 150).[400] [401] Patients were required to have moderate to severe depression without psychotic features for a duration of 4 weeks to 24 months, a score of ≥20 on the 17-item HAM-D (HAM-D-17), and a score of ≥2 on the depressed mood item (Item 1) of the HAM-D. *Lamictal* and DSP were titrated over 5 and 4 weeks, respectively to target doses of 200 mg once daily (QD) (Table 38).

Table 38. Dosing Schedule for *Lamictal* and Desipramine in Major Depressive Disorder Study [400] [401]

Week	Lamictal	Desipramine
1	25 mg QD	50 mg QD
2	25 mg QD	100 mg QD
3	50 mg QD	150 mg QD
4	50 mg QD	150 mg QD
5	100 mg QD*	200 mg QD*
6-8	200 mg QD*	200 mg QD*
9	0 mg/d, no taper	Taper†

BID = twice daily, d = day, mg = milligram, QD = once daily

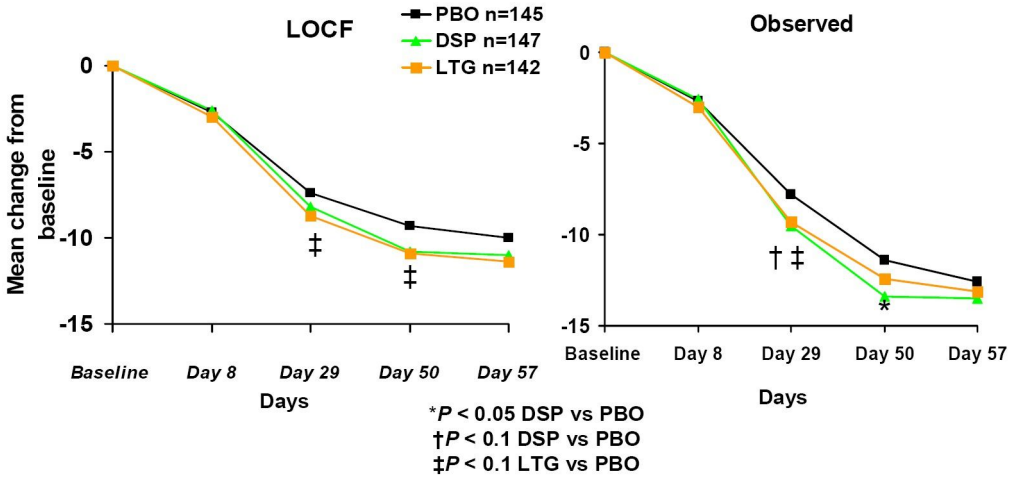
*BID dosing if intolerant (after Day 29) or decreased dose (after Day 36)

†If ≥3 weeks of DSP, tapered over 5-7 days, unless clinically inappropriate. DSP decreased to 100 mg/d x 3 days, 50 mg/d x 3 days, then stopped.

The primary efficacy measure was change from baseline of HAM-D-17 total score.[400,401] Secondary measures included HAM-D 31-item, HAM-D Item 1, MADRS, Clinical Global Impressions of Severity (CGI-S) and Improvement (CGI-I), and safety assessments. A response was defined as ≥50% reduction on the HAM-D-17 or MADRS scales or a rating of "much" or "very much" improved on the CGI-I scale. Treatment groups were comparable with respect to demographics and psychiatric history.

Patients receiving *Lamictal* and DSP experienced greater improvements versus PBO for all efficacy measures; however, these were not statistically significant for all timepoints and the mean change from baseline on HAM-D-17 was not significantly different from PBO for either treatment group (Figure). Statistically significant differences between patients receiving *Lamictal* and PBO were observed more frequently in the last observation carried forward (LOCF) analyses while significant differences between the groups receiving DSP and PBO occurred more frequently with the observed case analyses. Patients receiving *Lamictal* experienced significant improvement on CGI-S and CGI-I mean values LOCF versus PBO ($P \leq 0.05$); other LOCF measures, including HAM-D Item 1, HAM-D 31, and MADRS, showed trends for significance ($P \leq 0.1$). The trial lacked the sensitivity to statistically differentiate *Lamictal* or DSP from PBO, likely due to the high PBO response rate. Trough concentrations of both agents were roughly dose-proportional. No clear relationship was identified between HAM-D-17 mean score change from baseline and plasma concentrations for either agent.

Figure 31. HAM-D-17 Mean Score Change From Baseline Across Treament Groups[400]



The incidence of adverse events leading to withdrawal was 13% (n = 19), 21% (n = 31), and 10% (n = 15) for patients receiving *Lamictal*, DSP, and PBO.[400,401] No patient receiving *Lamictal* experienced a serious adverse event. Infection was the only commonly reported adverse event which occurred at a significantly higher rate in patients receiving *Lamictal* versus PBO[401] The incidence of rash for patients receiving *Lamictal*, DSP, and PBO were 8%, 10%, and 6%, respectively; one report, in a patient receiving PBO, was considered severe.[400] [401] There was no evidence for any effect of *Lamictal* on clinical chemistry or hematology parameters, vital signs, or body weight.[400]

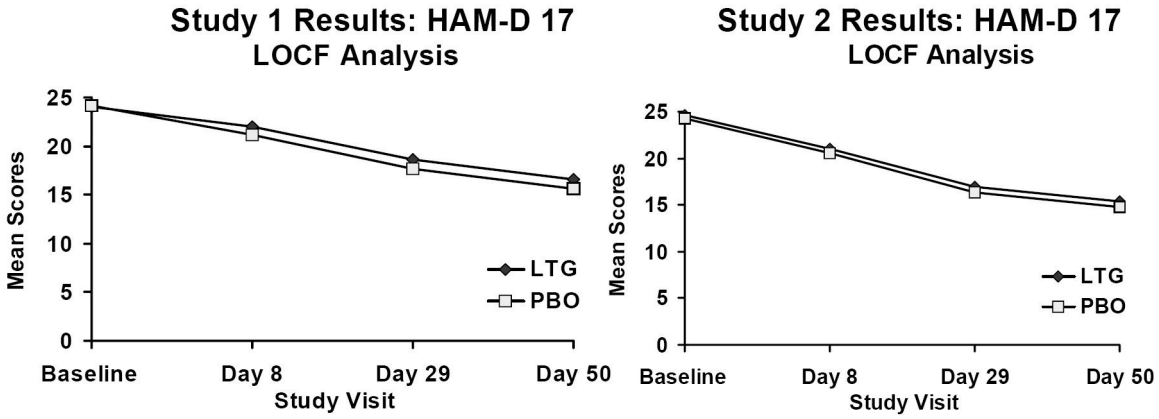
Two similar randomized, multicenter, placebo-controlled, double-blind, fixed-dose, 7-week trials were conducted to evaluate the antidepressant efficacy of *Lamictal* 200 mg/d as monotherapy in adult outpatients (mean age of 41 and 42 years) with recurrent MDD and currently experiencing a moderate to severe major depressive episode without psychotic features.[402,403] Inclusion criteria were similar to the previous trial. *Lamictal* was dosed once daily (BID if intolerant) 25 mg/d during weeks 1-2, 50 mg/d weeks 3-4, 100 mg/d week 5, and 200 mg/d weeks 6-7 (minimum of 100 mg/d if intolerant). Refer to Table 39 for patient characteristics and accountability.

Table 39. Number of Patients in Two Controlled Trials of Major Depressive Disorder [402] [403]

	Trial 1	Trial 2
Total Patients Randomized (n)	152	301
Lamictal	75	151
Placebo	77	150
Patients Completing Study n (%)	105 (69)	227 (75)
Lamictal	51 (68)	113 (75)
Placebo	54 (70)	114 (76)

The primary efficacy measure was the change from baseline HAM-D-17 at each study visit.[402,403] Secondary measures included HAM-D-31, HAM-D-Item 1, MADRS, CGI-S, CGI-I, the Quality of Life in Depression Scale (QLDS), and safety assessments. Neither trial demonstrated a significant difference in efficacy between *Lamictal* and PBO using primary or secondary efficacy variables ($P > 0.05$) (Figure). QLDS scores improved across both trials in patients receiving *Lamictal*, but did not reach statistical significance versus PBO at end of treatment.

Figure 32. Change in HAM-D-17 Scores (LOCF) from Baseline to Study Visits[402] [403]



The most commonly (≥10%) reported adverse events for either *Lamictal* or PBO, respectively, in either trial were headache (28% and 19% vs 27% and 21%), nausea (18% and 9% vs 8% and 9%), diarrhea (9% and 3% vs 16% and 7%), and infection (1% and 8% vs 5% and 11%).[402,403] Adverse events led to discontinuation in 9% and 3% of patients receiving *Lamictal* and PBO, respectively, in trial 1 versus 6% and 4%, respectively, in trial 2. No serious adverse events were considered reasonably attributable to *Lamictal*. Rash was reported in 9% and 5% of patients taking *Lamictal* in each trial versus 1% and 3% for PBO; none were considered serious. There was no evidence of clinical effect of *Lamictal* on vital signs or body weight.

controlled adjunctive trials

Barbee at el conducted a double-blind, placebo-controlled study to evaluate the efficacy and safety of *Lamictal* in combination with paroxetine for the treatment of refractory unipolar depression.[404] Adult patients (mean age 44 years; N = 183) with a diagnosis of unipolar major depression and a history of ≥ 1 prior failed adequate trial of an antidepressant were treated in an open-label phase for 8 weeks with paroxetine or paroxteine CR titrated to a maximum daily doses of 50 mg and 62.5 mg, respectively. At the end of the 8 week open-label phase, patients with a Hamilton Depression Rating Scale (HAM-D) score of ≥ 15 were randomized to receive *Lamictal* (n = 48) or placebo (PBO, n = 48) for a 10-week double-blind phase. *Lamictal* was initiated at 25 mg/day (d) and titrated over 8 weeks to a maximum dose of 400 mg/d. *Lamictal* did not separate from PBO on the Montgomery-Asberg Depression Rating Scale at the end of the double-blind phase (primary endpoint). The decrease in HAM-D scores over the double-blind phase was greater for patients receiving *Lamictal* (-7.32) compared to PBO (-7.04; $P < 0.05$).

The percentage of patient reporting adverse events during the double-blind phase was the same for both treatment groups (87.5%). The most common adverse events (> 5%) reported with *Lamictal* were headache, diarrhea, nausea, fatigue, urinary tract infection, rash, and excoriation. The rate of rash with *Lamictal* was 12.5% compared to 6.25% with PBO. There were no serious adverse events due to *Lamictal* and discontinuation rates were comparable between groups.

Normann et al evaluated the use of *Lamictal* in combination with paroxetine for acute depression in a double-blind, placebo-controlled clinical trial. [405] Adult patients (n = 40, age range 18-65 years) with a depressive episode by DSM-IV criteria (unipolar or bipolar) received *Lamictal* (n = 20) or placebo (PBO, n = 20) with a fixed-dose escalation scheme for 9 weeks along with paroxetine 20 mg QD from days 1-14 and 40 mg QD from days 15-63. Patients randomized to *Lamictal* were initiated at 25 mg/day (d) and titrated up to a final dose of 200 mg/d from days 43-63.

Adjunctive treatment with *Lamictal* did not result in a statistically significant difference in the primary endpoint (change from baseline in total HAM-D score) versus treatment with paroxetine alone. *Lamictal* demonstrated statistically significant ($P < 0.05$) efficacy versus paroxetine alone on core depressive symptoms as reflected by HAM-D items 1 (depressed mood), 2 (guilt feelings), and 7 (work and interest); and the CGI-S. Patients receiving *Lamictal* had faster onset of effect versus PBO with significant differences on some items noted as early as day 7. Patients receiving *Lamictal* had fewer treatment days

with benzodiazepines and fewer withdrawals for treatment failure versus PBO. Two patients receiving *Lamictal* developed neutropenia and 1 developed a benign rash. There was no detectable pharmacokinetic interaction between the drugs and plasma paroxetine levels did not differ significantly between the groups.

controlled adjunctive trial in patients with major depressive or bipolar ii disorder

Barbosa et al assessed augmentation treatment with *Lamictal* versus placebo (PBO) in 23 inpatients who had experienced ≥ 1 major depressive episode that was resistant to ≥ 1 prior trial of antidepressant therapy.[406] Patients diagnosed with major depressive disorder (MDD, n = 15) or bipolar II disorder (n = 8) were treated with fluoxetine (20 mg/day [d]) and randomly assigned to receive adjunctive *Lamictal* (n = 13) or PBO (n = 10) for 6 weeks. The dose of *Lamictal* was titrated from 25 mg/d to 100 mg/d. *Lamictal* was statistically superior to PBO on the CGI scale at endpoint, both in absolute terms (*Lamictal* 2.15 ± 1.28; PBO 3.40 ± 1.17; $P = 0.03$) and responder analysis (defined as CGI score of ≤ 2) (*Lamictal*, 84.6% [n = 11]; PBO, 30% [n = 3]; $P = 0.013$). The effect of *Lamictal* on CGI scores was seen in both MDD and bipolar II disorder. However, *Lamictal* failed to separate statistically from PBO on the HAM-D (primary endpoint) and MADRS; this may have been due to the small sample size and the limited statistical power of the study. One patient withdrew due to hypomania. No rashes were reported.

8.11

9. EVIDENCE TABLE

9.1 Epilepsy Pivotal Studies

Table 40. - See Appendix

9.2 Bipolar Pivotal Studies

Table 41. - See Appendix
Table 42. - See Appendix
Table 43. - See Appendix

10. OUTCOME AND ECONOMIC EVALUATION

10.1 Epilepsy

BACKGROUND

Economic Burden

The World Health Organization estimated that epilepsy was associated with $12.5 billion in total costs in the U.S. in 2000.[47] The average treatment-related cost of each new diagnosis of epilepsy in 1995 was: $2,642 during the first three months, $329 during the sixth year, and $6,429 total over six years.[46] The high cost at onset is attributed to diagnosis and initial treatment, then costs decline partly due to remission and AED discontinuation.

High indirect costs associated with epilepsy arise primarily from decreased productivity attributed to inefficiency at work (including work outside the home and within the household), missed days of work, unemployment, and premature death.[46] Indirect costs incurred by patients with epilepsy who are refractory to AEDs appear to be the primary drivers of the total costs of epilepsy.[48] In a 1995 analysis of the cost of refractory epilepsy in the U.S., indirect costs incurred by refractory patients accounted for two-thirds to three-fourths of total costs, which were estimated at $3.9 billion.

Due to the high rate of co-morbid disorders, it is difficult to compare health care utilization of patients with epilepsy to that of other chronic conditions or healthy patients. It is suspected, however, that epilepsy is associated with conditions that require more frequent healthcare utilization. One large survey-based study found that patients with epilepsy had higher depression scores and quality of life difficulties than patients with asthma or healthy controls. [407] Patients with epilepsy and untreated depression used significantly more health resources with and without adjustment for seizure type, seizure recency, and days with epilepsy symptoms.[408] Another study reported that patients with epilepsy and intellectual disability used secondary care services (outpatient activity) more frequently than patients with intellectual disability alone. [409]

Pharmacotherapy

In a prospective study, 525 patients with newly diagnosed epilepsy were followed over a 13-year period to assess their response to AED treatment. [410] Among the 525 patients, approximately two-thirds (63%) of patients remained seizure-free on AED medication or after their AED was discontinued. Persistent seizures were more likely to occur in those with symptomatic epilepsy than in those with idiopathic epilepsy (40% vs 26%) and in patients with more than 20 seizures before initiating treatment than in patients with fewer seizures (51% vs 29%). Seizure-free rates were similar between patients treated with monotherapy with an older AED (67%) and patients treated with monotherapy with a newer AED (69%). Among the 470 previously untreated patients, 47% became free of seizures (defined as no seizures for one year) with their first AED, and an additional 14% became seizure-free with their second or third drug.

According to the AAN/AES guidelines, patients with epilepsy typically remain on the initial or second therapy for several years. Because patients with epilepsy will respond to most drugs, treatment should include the AED that is most tolerable, has the lowest potential for harm, and has the least likelihood of negatively impacting quality of life. [51] In the Expert Consensus Guidelines for the treatment of Epilepsy in 2001, monotherapy was recommended as a first approach to treatment.[411] If this failed, most experts agreed that a second monotherapy should be tried next. Following this, there was not a clear distinction between additional trials of monotherapy and a combination of two AEDs.

Compliance

In a cross-sectional study of 54 patients with epilepsy, 59% were classified as nonaherent.[412] After excluding one patient who reported over 300 seizures per month, there was a significant positive correlation between adherence and absolute seizure frequency (r = 0.344, $P = 0.01$). In a retrospective, open-cohort study using Medicaid claims data from Florida, Iowa, and New Jersey (N = 33,658 or 525,114 total quarters), there were 26% nonadherent quarters, based on a medication possession ratio [MPR, defined as the proportion of days within an observation period covered by the total days supplied for a specific drug or class or drugs within the observation period (number of days between the first dispense date and the end of the days' supply of the last refill) or the number of days in quarters with supplies for an AED divided by the number of days in the quarter].[413] After multivariate adjustments, nonadherence was associated with > 3-fold increased risk of mortality compared to adherence (hazard ratio, HR = 3.32; 95% CI = 3.11 – 3.54) as well as a significantly higher incidence of emergency room (ER) visits (incident rate ratio, IRR = 1.50; 95% CI = 1.49 – 1.52), hospital admissions (IRR = 1.86; 95% CI = 1.84 – 1.88), motor vehicle accident injuries (IRR = 2.08; 95% CI = 1.81 – 2.39), and fractures (IRR = 1.21; 95% CI = 1.18 – 1.23) compared to periods of adherence. In a study of patients (n = 95, ages 16 - 64 years) with uncontrolled epilepsy in New Zealand, compliance failure was found to be instrumental in precipitating 31% of seizures. [414] At time of interview, 37% of patients were not taking their medication as prescribed. Additionally, findings from a random sample of adolescents (n = 232, aged 13-17 years) with epilepsy in Finland showed that only 22% were fully compliant with their AED regimen. [415]

A retrospective claims review of 10,892 patients with epilepsy revealed that a mean of 39% of patients were nonadherent, as defined by the MPR.[416] The mean MPR was highest for *Lamictal* (0.83; < 0.80 = nonadherent). Overall, AED nonadherence was associated with an increased likelihood of hospitalization (odds ratio [OR] = 1.110. $P = 0.013$), ER admission (OR = 1.479, $P < 0.0001$), and increased inpatient and ER costs ($P = 0.001$, both). Despite an offset of reduced prescription drug intake, a large net positive effect of nonadherence on total annual health care costs remained (+$1,466, $P = 0.034$). The net increase in annual healthcare costs was significantly larger in the elderly patients compared to the general study population (+$5,705, $P = 0.042$).

Results from a ten-year, U.S. community-based study of 127 adult patients with epilepsy (aged 18 – 59 years) estimated that 70% of patients self-regulated AEDs by forgetting one or more doses, increasing or decreasing the dosage, or discontinuing treatment completely.[417] The reasons cited included forgetting, wanting more seizure protection, disliking medication side effects, feeling they were doing well, and disliking the dependence of taking medication. Results from a community-based survey of patients with epilepsy (> 16 years) in the United Kingdom indicated that the strongest predictors of non-compliance were feeling it was not important to take AEDs as prescribed, being under age 60 (particularly adolescence), and receiving AED monotherapy.[418]

LAMICTAL

Economic Data

Adjunctive Therapy

Markowitz et al evaluated the direct costs and health outcomes in patients treated with *Lamictal* as adjunctive therapy versus older AEDs [phenytoin (PHY), carbamazepine (CBZ), valproate (VPA), and phenobarbital (PB)] for epilepsy in the U.S. [419] Effectiveness was measured by seizure-free days gained. Health care resource utilization measures included hospitalizations, outpatient and emergency department visits, surgery, and AEDs. Medical care use and cost estimates were derived from clinical trial data and published sources. The range of daily drug costs were estimated assuming the same average wholesale price (AWP), but a different daily dose of *Lamictal* (300 - 500 mg/day [d]; AWP $3.48 – $4.56). Costs and effectiveness (incremental costs per seizure-free days gained) of adjunctive therapy with *Lamictal* versus older AEDs were compared in refractory patients during three time periods: the first year of therapy, the second year (when decisions about surgery were made), and all subsequent years (Table 44). The cost-effectiveness model predicted that treatment with *Lamictal* would be associated with an overall reduction in use of other direct medical care resources (hospitalizations, outpatient visits, diagnostic and laboratory tests, and surgery).

Table 44. Annual Total Costs and Seizure-free Days Gained in Patients with Refractory Epilepsy Receiving AEDs over a 10-year Period [419]

Total Costs	Treatment With Older AEDs Only ($)	Treatment with Older AEDs and *Lamictal* ($)	Difference ($)	Seizure-free Days Gained with Adjunctive *Lamictal*
Year 1*	2,224	3,130	-906	10.8
Year 2†	14,146	10,560	3,586	31.2
Years 3-10‡	1,762	2,172	-410	25.1§

* Includes all patients starting on *Lamictal*

† Includes patients having a greater than 25% response to *Lamictal*

‡ Surgery was not considered in year one. Surgery refers to evaluation and surgical procedures in year two. Surgery refers to adjustment for surgery for years 3-10.

§ Adjusted downward to account for higher seizure reduction due to surgery in the group taking older AEDs only.

Cost-effectiveness of *Lamictal* during the first year resulted in a difference of $83.90 per seizure-free day gained while years 3-10 resulted in a difference of $16.3 per seizure-free day gained. [419] The 10-year cost and benefit totals (discounted at 3%) for a typical refractory patient started on *Lamictal* were analyzed. For the base case, total per patient costs over the 10-year period were estimated to increase by $728, and there were 106 more seizure-free days. This provided an estimate of $6.90 per seizure-free day gained. This base analysis of *Lamictal* resulted in a cost savings of $975 to an increase in $2,386 per year with incremental seizure-free days per year ranging from 38 to 174 days.

Messori et al conducted a retrospective lifetime cost utility study in which clinical data were derived from a placebo-controlled clinical trial, cost-of-illness data were drawn from at previous ad-hoc study, and quality-of-life values were obtained by prospectively interviewing a separate group of 81 patients with epilepsy. [420] The analysis showed that chronic treatment with *Lamictal* at doses of 500 mg/d implied an incremental lifetime cost of approximately $1,600,000 for every 100 patients. Incremental lifetime utility was approximately 40 quality-adjusted life-years (QALYs) for every 100 patients. On the basis of these data, adjunctive therapy with *Lamictal* was estimated to cost approximately $41,000 per QALY gained. Indirect costs were not included in this analysis. Other cost-effectiveness and cost-minimization studies have evaluated *Lamictal* versus newer AEDs (e.g. topiramate, gabapentin) as adjunctive therapy in the United Kingdom with mixed results. [421] [422,423] Seizure severity and frequency, adverse events and reasons for discontinuing AEDs were some of the measures included in these analyses. After six months of treatment in one study, the number of patients with >50% seizure reduction and patient satisfaction were similar between *Lamictal* and topiramate. [421] Annual indirect costs in British pounds (£) for *Lamictal* (£24) and gabapentin (£23) were similar in another study. [422] Response rates were similar between

Lamictal and topiramate in one study of pediatric patients with refractory partial seizures, however topiramate was associated with slightly higher QALY gains compared to *Lamictal*.[423]

Monotherapy

Economic data with *Lamictal* as monotherapy in patients with epilepsy has not been studied in the U.S.

Two separate cost-minimization analyses evaluated monotherapy with *Lamictal* versus older AEDs for the treatment of epilepsy in the United Kingdom. [424] [425] Drug costs, frequency of side effects, retention rates, medical consultations, inpatient, accident and emergency costs, laboratory investigations, and AED changes were some of the factors considered in these cost analyses. Indirect costs were not included. The direct medical costs of 2-years of therapy were £1,525-2,076 for *Lamictal*, £795-829 for CBZ, £736-768 for PHY, and £868-884 for VPA in one analysis [424], while a separate analysis showed the average annual cost per patient was £522 for *Lamictal* and £179 for CBZ. [425]

Substitution of Formulation

Data regarding the economic impact of generic substitution for lamotrigine are limited. A retrospective database study of medical and pharmacy claims based in Quebec (April 1998 to July 2006) by LeLorier et al evaluated switchback rates and medical services utilization secondary to generic substitution of antiepileptic drugs (AEDs), including *Lamictal*, compared to non-AEDs in patients with epilepsy. A subanalysis of these claims (August 2002 and July 2006) evaluated the economic impacts of generic substitution of lamotrigine in Canada and extrapolated the Canadian costs to a United States (US) setting. At the time this study was conducted, generic lamotrigine was not available in the US. Healthcare costs ($ per person per year) were compared during periods of branded and generic use of lamotrigine. Two cost conversion methods were utilized; one used purchasing power parities, US/Canada service use ratios, and exchange rate, and another used Canadian health care utilization and US unit costs. In the subanalysis, the mean age of the patients was 39 years. Patients were observed for 1650.9 and 291.2 person-years of branded and generic use of lamotrigine, respectively.

Of 671 patients taking *Lamictal*, the switch rate (cumulative probability of a patient switching to the generic formulation) was 27.9%. Additionally, the switchback rate (cumulative probability of a patient switching back to branded *Lamictal*) was 27.5%. Generic use periods were associated with significantly higher daily doses of lamotrigine (+5.1%, 251 mg vs. 239 mg, respectively; $P < 0.001$), higher number of dispensations for other AEDs (23.9 vs. 20.4 per person per year, respectively; $P < 0.0001$), higher non-AED dispensations (32.8 vs. 26.4 per person per year, respectively; $P < 0.0001$), higher incidence rates of medical services (9.8 vs. 8.7 visits per person per year, respectively; $P < 0.0001$), and longer hospital stays (4.9 vs. 3.3 days per person per year, respectively; $P < 0.0001$) compared to periods of branded use.[426]

Using the first cost conversion method stated above, the total projected adjusted cost of health care services was $602 (US) per person per year higher during periods of generic use compared to brand use (P = NS, not significant). The aggregation of all estimated health care costs resulted in a statistically significant adjusted cost difference of $1758 (US) between periods of generic and branded use ($P = 0.012$), despite the lower acquisition cost of generic lamotrigine [cost difference -$1175 (US) for generic vs. brand lamotrigine; $P < 0.001$] .

The second cost conversion method showed that the total projected adjusted cost of health care services was $574 (US) per person per year higher during periods of generic use compared to brand use (P = NS). The overall estimated health care costs demonstrated a statistically significant adjusted cost difference of $2516 (US) between periods of generic and branded use ($P = 0.004$), despite the lower acquisition cost of generic lamotrigine [cost difference -$1942 (US) for generic vs. brand lamotrigine; $P < 0.001$].

Both cost conversion methods demonstrated that the main driver of medical cost differences between the brand and generic periods were higher costs associated with longer length of hospital stay during the generic period [Method 1 adjusted cost difference $1196 (US); P=0.066; Method 2 adjusted cost difference $1841 (US); P=0.026].[427] The higher overall health care costs seen during the generic period exceeded the projected savings associated with the use of generic lamotrigine.

Marson et al conducted two, prospective, open-label, controlled trials to compare standard and newer antiepileptic drugs (AEDs) as monotherapy in epilepsy.[313] Outpatients in the United Kingdom, > 4 years of age, with a history of ≥ 2 clinically definite unprovoked partial (Arm A) or generalized seizures

(Arm B) in the previous year were included (including newly diagnosed patients, patients who failed monotherapy, and patients who had achieved remission but relapsed after discontinuation of treatment). Primary outcome measures for both studies included time to treatment failure (drug discontinuation due inadequate seizure control or intolerable adverse events, or both, OR addition of other AEDs, whichever occurred first) and time to 1-year remission of seizures.

Arm A of the trial compared *Lamictal*, carbamazepine (CBZ), gabapentin (GBP), oxcarbazepine (OXC), or topiramate (TPM) in 1721 patients with partial onset seizures and unclassifiable epilepsy.(313) (314) The health economics analysis (secondary endpoint) was performed with two distinct incremental cost-effectiveness ratios: cost per quality adjusted life year (QALY) gained and cost per seizure avoided. The first analysis compared *Lamictal*, CBZ, GBP, and TPM and included all 636 adult patients who were randomized and provided complete EuroQol (EQ-5D) responses. Based on incremental cost and QALY gains, *Lamictal* was more cost effective than OXC or TPM. The incremental cost-effectiveness ratio for *Lamictal* relative to CBZ was £ 11,851. The second analysis compared *Lamictal*, CBZ, GBP, OXC, TPM and included 414 adults who provided complete EQ-5D responses. Both TPM and GBP had positive incremental costs and negative incremental QALY gains and were dominated by OXC and *Lamictal*, respectively.

Two analyses were conducted to determine cost per seizure avoided. The first analysis compared *Lamictal*, CBZ, GBP, and TPM, and included 823 children and adults for whom data was collected for both numbers of seizures and resource use. TPM and GBP had positive incremental costs and negative incremental number of seizures avoided, and were dominated by CBZ and *Lamictal*, respectively. The second analysis compared *Lamictal*, CBZ, GBP, OXC, and TPM, and was based on 547 adults and children. *Lamictal*, TPM, and GBP had positive incremental costs and negative incremental seizures avoided and were dominated by OXC.

Arm B of the trial compared *Lamictal*, valproate (VPA), or TPM in 716 patients with generalized or unclassifiable epilepsy.(314) The cost per QALY analysis was based on 165 adult patients who provided complete EQ-5D responses at 2 years. *Lamictal* had a positive incremental cost and a negative incremental QALY gain and was dominated by TPM. The cost per seizure avoided analysis was based on 299 adults and children for whom data on seizures and resource use was available. TPM and *Lamictal* had positive incremental costs and negative incremental seizures avoided and were dominated by VPA. In both analyses, the same pattern of results was noted when different combinations of high and low costs for VPA and *Lamictal* were evaluated.

10.2 Bipolar

BACKGROUND

Economic Burden

In 1990, the World Health Organization, identified bipolar disorder as the sixth leading cause of disability-adjusted life years in the world among people aged 15-44 years.(77) Bipolar disorder is associated with significant direct and indirect costs. (428) (429) In 1998, the direct and indirect lifetime medical costs related to bipolar disorder were estimated at $24 billion.(80) In the same study, reported lifetime direct costs was $13 billion, representing 55% of total costs. In a study of patients insured through a large staff-model health maintenance organization in 1995 - 1996, healthcare costs for patients with bipolar disorder exceeded those for patients treated for major depression or diabetes. (81) These costs were driven by disproportionately high use of specialty mental health services, substance abuse treatment, and inpatient care. In another review of expenditures from employer-sponsored insurance claims in 1996, the hospital admission rate for patients with bipolar disorder was 39.1% compared with 4.5% for all other behavioral health claimants. (79) In a retrospective cohort study of elderly patients, patients with bipolar disorder (n = 37, mean age 69.7 years) used nearly four times as many mental health services and were four times more likely to have a psychiatric hospitalization than patients with major depressive disorder (unipolar depression; n = 85, mean age 71 years).(430) Another study demonstrated that patients with bipolar disorder utilized 3-4 times more healthcare resources compared with non-bipolar patients over one year period ($7663 versus $1962, respectively).(431)

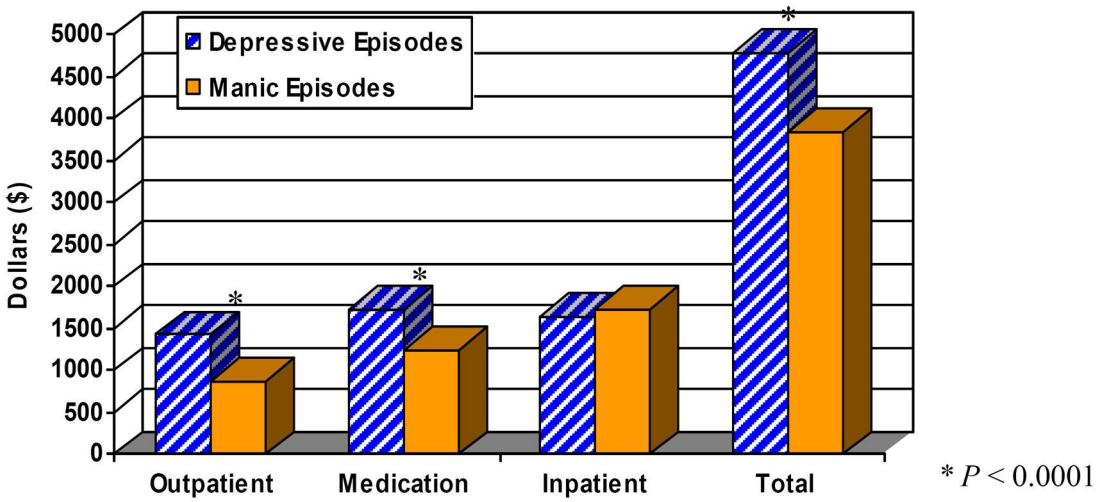
Bipolar Depression versus Mania

Patients with initial symptoms of bipolar depression were more likely to have frequent recurrences compared to those reporting manic or hypomanic initial symptoms. [56] Since some patients in mixed episodes resemble depressed patients in self-reported quality of life; it appears that depressive symptoms drive perception of quality of life. [432] In a prospective, natural history study of patients with bipolar I disorder with a mean follow-up of 12.8 years, patients spent nearly half of their time symptomatically ill.[59] Depressive symptoms (31.9% of total follow-up weeks) predominated over manic/hypomanic symptoms (8.9% of weeks) or cycling/mixed symptoms (5.9% of weeks). In a naturalistic study of 155 patients with bipolar disorder, 93% of manic patients had recovered by 18 months compared with 78% of the depressed patients and 68% of mixed and cycling patients. [433]

In a retrospective study of 2883 patients with bipolar disorder covered by a large private insurer in northeastern United States in 1997, a diagnosis of bipolar depression was associated with higher healthcare resource consumption compared to mania.[431] Additional analyses of costs found that bipolar depression was associated with greater annual medical encounter costs ($5130 per patient) compared with mania ($4775 per patient). The increased costs were due to hospitalizations, physician visits, emergency room care, and mental and non-mental health care.

In a retrospective study using a United States managed care claims database (N = 38,280, mean age 39 years) from 1998 to 2002, Fu et al found the annual outpatient and inpatient costs to managed care payers were fourfold and twofold higher, respectively, for patients with bipolar depression than for patients with mania.[434] Annual hospitalizations were eight times more common for bipolar depression than mania and 80% of all outpatient visits were for bipolar depression. Additionally, depressive episodes occurred three times more frequently (n = 3,083) than manic episodes (n = 1,236). The unadjusted average outpatient, medication and inpatient costs for a depressive episode were $1426, $1721, $1646 compared to $863 ($P <$ 0.0001), $1248 ($P < 0.0001$), $1736 ($P = 0.54$) for a manic episode (Figure 33). The total cost of a bipolar depressive episode ($5503) was approximately twice that of a manic episode ($2842) after controlling for age, gender, length of episode, site of index visit and pre-episode costs.

Figure 33. Unadjusted Mean Cost per Episode[434]



These studies indicate that bipolar depression is more difficult and expensive to treat than mania. Therefore, preventing or delaying bipolar depressive episodes could result in substantial cost-savings to a managed care payer.

Pharmacotherapy

According to the most recent American Psychiatric Association (APA) practice guidelines for the treatment of bipolar disorder, treatment should include both 1) managing acute episodes, where the primary goal is to achieve remission and 2) maintenance, where the primary goal is to prevent or delay the recurrence of mood episodes. [82] In 1998, Begley found that medication costs accounted for the highest proportion of

direct costs (46%).[80] The medication costs for the treatment of bipolar disorder comprised only 0.3% of the total cost and 1.7% of the direct costs of bipolar disorder in 1991. [429] Simon and Unützer found that in a managed care setting, psychotrophic costs were $329 on average per year for patients with bipolar disorder and $113 for patients with major depressive disorder. [81] Some of these medication costs have included laboratory costs such as testing for blood levels while other studies have separated laboratory costs as an additional category of direct medical costs. Therefore, effective pharmacotherapy for bipolar disorder may reduce costs associated with recurrent mood episodes.

Effective treatment for bipolar disorder may also reduce the economic burden to society. A survey of bipolar members of the National Depressive and Manic-Depressive Association found that compared with untreated or inadequately treated individuals with bipolar disorder, those receiving effective treatment committed fewer minor crimes (8% vs 27%); had fewer financial difficulties (36% vs 57%), experienced less marital problems and divorces (32% vs 59%); suffered fewer injuries to themselves or others (11% vs 35%); experienced less alcohol and drug abuse (13% vs 41%); and had fewer excessive gambling problems (3% vs 7%) ($P < 0.01$). [56]

Minimizing the adverse effects of treatment and enhancing patient adherence to pharmacotherapy are long-term maintenance goals of bipolar I disorder. [82]

A growing body of evidence has established the relationship between obesity and mental health disorders. [435] McElroy et al retrospectively reported 58% of patients (n = 644) with bipolar disorder studied were overweight, 21% were obese, and 5% were extremely obese. [436] However, conflicting evidence exists in this area. [437] Some antipsychotics used to treat bipolar disorder have been reported to induce weight gain.[438] [439,440]

A favorable tolerability profile and convenient dosing regimen offer treatment compliance advantages for patients in the long-term management of bipolar disorder. Non-compliance with maintenance treatment is the most frequent cause of mood episode recurrence and leads to poor outcomes, including increased levels of suicidal behavior. [441] Of 1036 patients prescribed maintenance treatment with mood stabilizers in a large health maintenance organization database (1995 - 1996), over 75% had a treatment interruption in a one-year period and most patients (68%) who discontinued maintenance treatment required a mental health clinic visit within 90 days.[442]

Conversely, compliant use of maintenance medications for bipolar disorder may be associated with fewer admissions to clinics and reduced total cost. Armond et al found that 61% of patients with bipolar disorder receiving lithium maintenance treatment had no further hospital admissions and 86% had fewer admissions compared with patients that received acute treatment only. [443] Additionally, maintenance therapy with lithium conferred employment and personal relationship benefits. A study of the relationship between non-compliance with treatment and inpatient visits and costs among severely mentally ill patients using claims data from a Wisconsin mental health system database from 1989 to 1990 (n = 619) found that 33% of patients with bipolar disorder were non-compliant compared with 31% of patients with schizophrenia and 41% of other severely mentally ill patients. [444] The total non-compliant patient population had higher rates of hospitalization compared with the compliant population (42% vs 20%) as well as longer duration of inpatient visits (16 days vs 4 days) and higher hospital costs ($3993 vs $1048).

LAMICTAL

Economic Data

Using a United States managed care claims database (1997 – 2001), Simons et al compared outcomes for the 12 months before and 12 months after initiation of *Lamictal* in patients with bipolar disorder previously treated with lithium, other anticonvulsants, or antidepressants. [445] Following initiation of *Lamictal*, a statistically significant reduction in hospitalization duration due to acute depression was found in patients previously treated with lithium and valproate/carbamazepine. Additionally, medical costs were lower after the initiation of *Lamictal* in patients previously treated with lithium, valproate/carbamazepine, and antidepressants (Table 45). The net change in medical costs for patients receiving *Lamictal* was -$1257, while the net change in medication costs was $834, resulting in a total net savings of $423 per patient per year to the managed care payer. Hospitalization duration due to acute depression was significantly reduced after initiation of *Lamictal* in patients previously treated with lithium and valproate/carbamazepine.

Table 45. Change in Cost Associated with Depressive or Manic Episode following Initiation of *Lamictal* (27)

	Lithium (n = 32)	Carba-mazepine/Val-proate (n = 50)	Other anticonvulsants (n = 58)	SSRIs (n = 105)	Other antidepressants (n = 81)
Depression costs ($)	**-2,036***	**-305**	**257**	**-435**	**-353**
Mania costs ($)	**-520***	**104**	**-97**	**-138**	**-19**
* $P \leq 0.05$; SSRIs = Selective serotonin reuptake inhibitors					

For a defined cohort of adult patients with bipolar I disorder experiencing a recent episode of mania, the Markovian model indicated that *Lamictal,* lithium, and olanzapine were all cost-effective compared to no maintenance treatment.(446) *Lamictal* was shown to be more effective and less costly than olanzapine in the base case and the use of *Lamictal* was predicted to reduce hospital bed days versus lithium. Future research will examine the impact of suicide and indirect healthcare costs on cost-effectiveness of these agents.

11. ECONOMIC IMPACT MODEL

BACKGROUND

The efficacy of *Lamictal* as monotherapy as maintenance treatment of bipolar I disorder was established in two multicenter, double blind, placebo controlled, 18-month studies.(10,11) These studies assessed the efficacy and tolerability of *Lamictal* and lithium as monotherapy compared with placebo for delaying time to intervention for a mood episode. The study by Bowden et al enrolled adult patients with bipolar I disorder who presented with a current or recent (within 60 days) manic or hypomanic episode and the other by Calabrese et al enrolled currently or recently (within 60 days) depressed patients. In order to evaluate the cost-effectiveness of *Lamictal* compared with olanzapine, the base case model was restricted to patients with a recent manic episode, since this was the only available data for maintenance therapy with olanzapine.(10) (447)

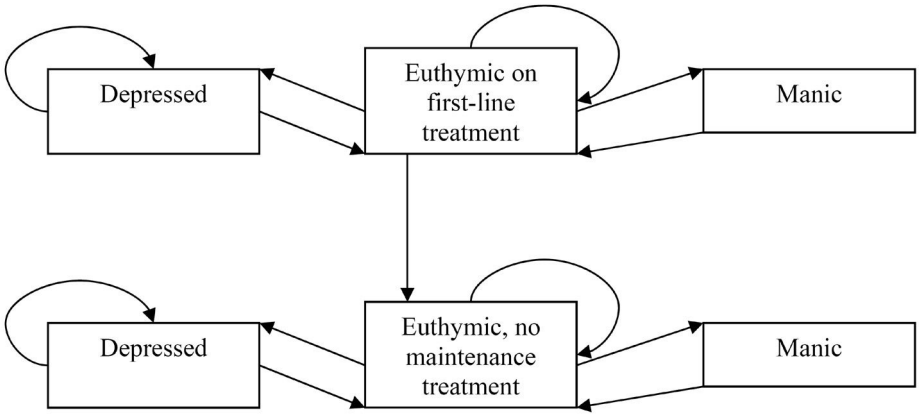
PURPOSE

The objective of this model of cost-effectiveness was to estimate the impact on health outcomes and cost consequences of no maintenance treatment compared to *Lamictal* and other commonly used treatments in the management of recently manic patients with bipolar I disorder in the United State (U.S.).

METHODS

A Markov model was constructed based around the three mood states of euthymia, mania, and depression.(446) The model structure is depicted in Figure 34. The model simulated a cohort of 1,000 patients with bipolar I disorder who were recently stabilized after resolution of a manic episode. All patients in the cohort are initially assigned to the euthymic mood state. By the end of the first cycle in the model, patients either remain euthymic, move into mania or depression, or ‘drop out’ of first line therapy into ‘no treatment’. The transitional probabilities for patients transferring to other mood states during a cycle are assumed to be constant over time, irrespective of patient history, consistent with Markovian assumptions. The model follows the cohort for 18 months. The model estimated the clinical and economic outcomes in patients receiving *Lamictal*, olanzapine, lithium and no maintenance treatment (assumes acute treatment only).

Figure 34. Schematic Representation of the Quarterly Markov Model Structure[446]



Transitional Probabilities

Consistent with Markov modeling principles, the transitional probabilities were assumed equal over the six quarterly time periods of the model.[446] For example, for a given treatment option, if X% of patients completed after 18-months, then the quarterly probability of being event free in a given quarter was estimated as $X^{1/6}$. The residual probability was then assigned across the other events in proportion to the size of the 18-month event risks.

Event probabilities from the study by Bowden et al were used to derive the quarterly transitional probabilities used in the model (Table 46).[10,446] The transitional probabilities for patients transferring to other mood states during a 3-month cycle were assumed constant over time, regardless of patient history. Placebo results were used as a proxy for the modeled "no-maintenance" treatment group. Data from patients who withdrew from the study due to an adverse event or consent withdrawal were used to proxy patients who stop maintenance therapy and transition to the no maintenance therapy state.

The transitional probabilities for olanzapine were derived from a double-blind, placebo-controlled 12-month study. [447] Other olanzapine studies were identified, but did not meet selection criteria. Given the broad comparability of the studies conducted by Tohen et al and Bowden et al in terms of inclusion criteria and outcomes, olanzapine was included in the model to anchor the results from Tohen et al to those from Bowden et al using the placebo results from the two studies.[446] The model estimated risk ratios of modeled events for patients receiving olanzapine compared with placebo. In an attempt to allow for differences in patient populations in the two studies, these risk ratios were then multiplied by the absolute placebo rates from the study by Bowden et al. Because the placebo rate for completers was zero in the study by Bowden et al, an arbitrary completer rate of one was assumed in order to estimate a completer rate for olanzapine. The resulting risk probabilities for olanzapine were then converted to constant Markov quarterly transitional probabilities.

Table 46. Quarterly Transitional Probability Estimates Across Treatment Groups [446]

Quarterly Transitional Probability	No Maintenance Treatment	Lithium	*Lamictal*	Olanzapine
P (become manic in a given quarter)	0.592	0.111	0.215	0.116
P (become depressed in a given quarter)	0.408	0.143	0.071	0.168
P (remain euthymic)	0	0.561	0.655	0.617
P (adverse event or withdrew consent)	-	0.185	0.059	0.099

Resource Utilization

The model takes a direct healthcare costing perspective (based on US dollars in 2004).[446] Modeled resource use items include drug costs for maintenance treatment, drug and hospitalization costs for the treatment of acute manic and depressive episodes, and costs of associated contacts with healthcare

professionals for monitoring and pathology tests. Some resource use variables including percentage of acute patients hospitalized, length of hospital stays, and frequency and length of monitoring visits were estimated using responses from a GlaxoSmithKline sponsored physician survey.

Quality Adjusted Life Years (QALYs)

Health state utility values were estimated using the 36-item short form (SF-36) values collated as part of the two maintenance studies of *Lamictal*, converted to utility values using a standard algorithm and using values from published literature.[448] [449] Consequently, our analysis assumed utility values of 0.8, 0.7 and 0.4 for euthymic, manic, and depressive mood states, respectively.[446]

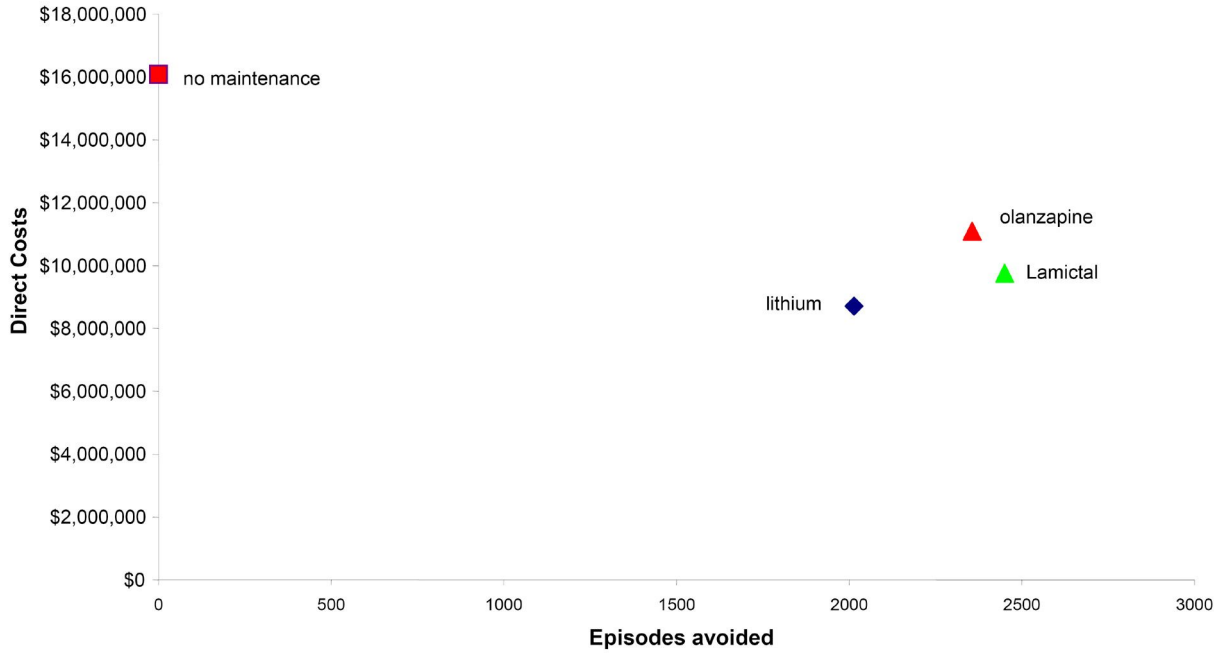
MODEL RESULTS

Outcomes from the model are presented in Table 47 and Figure 35. The model indicated that treatment with Lamictal avoided the most depressive and acute mood (manic and depressive combined) episodes, provided the most euthymic days and gained the most QALYs versus the lithium, olanzapine, or no maintenance treatment.[446] Treatment with olanzapine avoided the most manic episodes. Lithium was the least costly option in terms of direct healthcare costs. In the base case, all evaluated maintenance therapies were found to be cost-effective compared to the no-maintenance treatment option. *Lamictal* had incremental cost-effectiveness ratios (ICER) of $30 per euthymic day and $2,400 per acute episode avoided compared with lithium. *Lamictal* was found to be more effective and less costly than olanzapine. The use of *Lamictal* compared to lithium reduced demand for hospital beds through fewer admissions for depressive episodes.

Table 47. Outcomes and Total Costs for 18-months Observation Across Treatment Groups for 1000 Patient Cohort [446]

	Lamictal **1st Line**	**Lithium 1st Line**	**Placebo**	**Olanzapine**
Manic episodes (number)	1418	1313	2644	1030
Depression episodes (number)	598	1140	1822	1080
Total mood episodes (number)	2016	2453	4466	2110
Direct total costs (US dollars)	$9,755,052	$8,709,608	$16,083,654	$11,092,542
Days in euthymic state	463,789	429,313	339,986	441,485
Days in manic state	42,549	39,386	79,320	30,900
Days in depressive state	41,162	78,801	128,193	75,115

Figure 35. Cost-Effectiveness Frontier: Cost per Acute Mood Episode Avoided Across Treatment Groups[446]



Sensitivity Analysis

Sensitivity analysis was used to explore the relative sensitivity of the results to changes in the input variables.[446] The ICER for *Lamictal* compared with lithium is sensitive to variables which affect only the outcomes associated with *Lamictal*; particularly if variables simultaneously increase the numerator (incremental costs) and decrease the denominator (incremental effectiveness) and vice versa. As such, it is most sensitive to the transitional probabilities and the price of *Lamictal*. For these reasons, the modeled ICERs were most sensitive to the transitional probabilities which represented the risk of patients experiencing an acute mood episode. The ICERs were less sensitive to variables which simultaneously impact on the alternative treatment outcomes. For example, in the threshold sensitivity analysis, even assuming extreme values for some variables (e.g. the assumed manic inpatient LOS or proportion of patients hospitalized) would not achieve the threshold value. Threshold analysis also illustrated that the base case result that *Lamictal* was superior to olanzapine is sensitive to changes in input assumptions.

As previously stated, the model used effectiveness data from the study by Bowden et al which included patients with a current or recent manic/hypomanic episode. Replacing the effectiveness data with that from the Calabrese trial (patients with a current or recent depressive episode) produced a less optimistic economic result for *Lamictal* compared with lithium, although *Lamictal* remained clinically more effective. Over the 18-month period modeled, treatment with lithium was the least costly treatment option at $2.7 million (m) per year, followed by the 'no maintenance treatment' option ($3.8 m), and *Lamictal* ($4.4 m). Treatment with *Lamictal* resulted in the fewest depressive episodes (n = 732) compared with lithium (n = 803) and 'no maintenance treatment' (n = 1087). The number of manic episodes was 174 for lithium, 288 for *Lamictal*, and 364 for 'no maintenance treatment'. *Lamictal* achieved the most QALYs (n = 1142) compared to lithium (n = 1137) and 'no maintenance treatment' (n = 1113).

SUMMARY OF MODEL RESULTS FOR LAMICTAL

For a defined cohort of adult patients with bipolar I disorder experiencing a recent episode of mania, the Markovian model indicated that *Lamictal*, lithium, and olanzapine were all cost-effective compared to no maintenance treatment.[446] *Lamictal* was shown to be more effective and less costly than olanzapine in the base case and the use of *Lamictal* was predicted to reduce hospital bed days versus lithium. Future research will examine the impact of suicide and indirect healthcare costs on cost-effectiveness of these agents.

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Appendix

Table 40. Pivotal Trials for *Lamictal* in the Treatment of Epilepsy

Citation	Duration	Study Design	Dosing	Endpoints	Results
Adjunctive Therapy For Partial Seizures In Adults					
Matsuo et al [3]	•24-week	•Placebo-controlled •Double-blind •Parallel-design •Dose comparison •Adjunctive trial •216 adults with refractory partial seizures	•LTG 300 mg/d (n=71) or 500 mg/d (n=72) or PBO (n=73) added to 1-3 other AEDs; No VPA	•Primary: •Seizure frequency •Secondary: •Number of days with seizures •Patient's clinical status	•Median reduction in all partial seizures •300 mg/d: 20% •500 mg/d: 36% ($P = 0.007$ vs PBO) •PBO: 8% •34% of patients receiving 500 mg/d experienced >50% reduction in number of seizures •Reduction in seizure days: •300 mg/d: 21% •500 mg/d: 26% ($P < 0.05$) •PBO: 15% •Commonly reported adverse events: •300 mg/d: diplopia (24%), somnolence (21%), pain (13%) •500 mg/d: dizziness (54%), diplopia (49%), ataxia (28%), blurred vision (25%), nausea (25%), vomiting (18%)
Messenheimer et al [4]	•Two 14-week treatment periods (last 2 wks for dose tapering) •4-week wash out	•Placebo-controlled •Double-blind •Crossover-design •Adjunctive trial •98 adults with refractory partial seizures	•LTG 400 mg/d (n=94) or PBO (n=96) added to up to 2 other AEDs; No VPA	•Primary: •Seizure frequency •Secondary: •Number of days with seizures •Patient's clinical status	•25% median decrease in seizure frequency (20% of patients had ≥50% reduction) vs. PBO ($P < 0.001$) •18% median decrease in seizure days •15% of patients had 50% reduction vs. PBO •Commonly reported adverse events with LTG: •Ataxia (32%), dizziness (31%), diplopia (18%), somnolence (16%), rash (15%)
lamotrigine (LTG); valproate (VPA); antiepileptic drug (AED); placebo (PBO); week (wk); kilogram (kg); phenytoin (PHT); carbamazepine (CBZ); felbamate (FBM); gabapentin (GBP); primary generalized tonic-clonic (PGTC)					

Citation	Duration	Study Design	Dosing	Endpoints	Results
Schapel et al [2]	•Two 12-week treatment periods •4-week wash out	•Placebo-controlled •Double-blind •Crossover-design •Adjunctive trial •41 adult patients with refractory seizures	•Patients on VPA (n=13) received LTG 150 mg/d; other patients (n=28) had a target dose of LTG 300 mg/d or PBO added to 1-2 other AEDs	•Primary: •Seizure frequency •Secondary: •Number of days with seizures •Patient's clinical status	•Reduction in total seizure count was 63% with LTG vs. 34% PBO •22% (LTG) vs. 0% (PBO) experienced a ≥50% reduction in seizure count •66% (LTG) vs. 24% (PBO) experienced a reduction in seizure days •Efficacy trend suggested in secondarily generalized seizures (non-significant) •Commonly reported adverse events with LTG: •Ataxia (17%), dizziness (17%), nausea (17%), rash (15%)
Adjunctive Therapy For Partial Seizures In Pediatric Patients					
Duchowny et al [5]	•Baseline phase: 8 wks •Treatment phase: 18 wks: •6-week dose escalation •12-week maintenance period •Taper and follow-up: 1 - 6 wks (depending on treatment dose)	•Placebo-controlled •Double-blind •Adjunctive trial •199 patients with inadequately controlled partial seizures (aged 2 – 16 years)	•Patients randomized to receive adjunctive treatment with LTG (1-15 mg/kg/d) (n=98) or PBO (n=101) •Dose escalation based on concomitant medications; No FBM or GBP	•Primary: •Median reduction of all partial seizures over entire treatment period •Secondary: •Median reduction of secondarily generalized seizures	•36% (LTG) vs. 7% (PBO) reduction of all partial seizures ($P = 0.008$) for weeks 1-18 •53% (LTG) vs. 9% (PBO) reduction in secondarily generalized seizures ($P = 0.003$) •Adverse events reported more frequently with LTG vs PBO included dizziness (21% vs 5%), tremor (12% vs 2%), nausea (11% vs 2%), and ataxia (10% vs 2%).
Adjunctive Therapy For Seizures Of Lennox-Gastaut Syndrome					
lamotrigine (LTG); valproate (VPA); antiepileptic drug (AED); placebo (PBO); week (wk); kilogram (kg); phenytoin (PHT); carbamazepine (CBZ); felbamate (FBM); gabapentin (GBP); primary generalized tonic-clonic (PGTC)					

Citation	Duration	Study Design	Dosing	Endpoints	Results
Motte et al [7]	•Baseline phase : 4 wks •Treatment phase: 16 wks	•Placebo-controlled •Double-blind •Adjunctive trial •169 patients with inadequately controlled LGS (aged 3 –25 years)	•LTG (n=79) or PBO (n=90) added to up to 3 other AEDs Patients taking VPA: •≤25kg: 50-100mg/d (mean dose 13 mg/kg/d) •>25kg: 100-200 mg/d (mean dose 8.4 mg/kg/d) Patients not taking VPA: •≤25kg: 200-300 mg/d (mean dose 3.7 mg/kg/d) •>25kg: 300-400 mg/d (mean dose 3.7 mg/kg/d)	•Primary: •Median reduction of all major seizures •Secondary: •Parent/care giver evaluations •Quality of life	•32% (LTG) vs. 9% (PBO) experienced a median reduction in all major seizures (*P* = 0.002) •33% (LTG) vs. 16% (PBO) experienced a ≥50% reduction from baseline in all seizure types (*P* = 0.01) •17% (LTG) vs 3% (PBO) experienced an increase in seizure-free days •Atypical absence seizures were not significantly reduced •Parent/care giver evaluations showed greater improvement in general health for patients receiving LTG (73%) vs. PBO (50%) •Quality of life measures showed improvement in mood for patients receiving LTG •Adverse events: Colds and pharyngitis reported more frequently with LTG vs PBO •Rash: LTG (n=7), PBO (n=6) •Rash led to withdrawal: LTG (n=2), PBO (n=1)
Adjunctive Therapy For Primary Generalized Tonic-Clonic Seizures					
lamotrigine (LTG); valproate (VPA); antiepileptic drug (AED); placebo (PBO); week (wk); kilogram (kg); phenytoin (PHT); carbamazepine (CBZ); felbamate (FBM); gabapentin (GBP); primary generalized tonic-clonic (PGTC)					

Citation	Duration	Study Design	Dosing	Endpoints	Results
Biton et al [6]	•Screening (≤ 2 wks) •Baseline (8 wks) •Escalation (12 wks for patients 2-12 years or 7 wks for patients >12 years •Maintenance: 12 wks	•Placebo-controlled •Double-blind •Adjunctive trial •117 patients with ≥3 PGTC seizures (2-55 years of age) during 8 wk baseline phase	•LTG (n=58) or PBO (n=59) added to up to 2 other AEDs •Target doses based on concomitant AED: •3 mg/kg/d - 12 mg/kg/d (2-12 years of age) •200 mg/d - 400 mg/d (>12 years of age)	•Primary: •Median % reduction in monthly PGTC seizures •Secondary: •Additional seizure endpoints •Adverse events	•Median percent reduction in PGTC seizure frequency was 66% (LTG) vs 34% (PBO) during escalation + maintenance phases ($P = 0.006$) •Similar pattern of results was observed for all generalized seizures •Median PGTC seizure counts per month also significantly decreased •0.95 (LTG) vs 2.29 (PBO) during escalation ($P = 0.013$) •0.42 (LTG) vs 1.61 (PBO) during maintenance ($P = 0.001$) •Adverse events: dizziness (5% LTG, 2% PBO), somnolence (5% LTG, 2% PBO), nausea (5% LTG, 3% PBO) •Withdrew due to adverse events: •n=5 (LTG), including 1 case of non-serious rash •n=2 (PBO)
Conversion To Monotherapy From CBZ, PHT, PB, Or PM As The Single AED In Adults With Partial Seizures					
lamotrigine (LTG); valproate (VPA); antiepileptic drug (AED); placebo (PBO); week (wk); kilogram (kg); phenytoin (PHT); carbamazepine (CBZ); felbamate (FBM); gabapentin (GBP); primary generalized tonic-clonic (PGTC)					

Citation	Duration	Study Design	Dosing	Endpoints	Results
Gilliam et al [8]	•Transition period: 8 wks •Monotherapy phase: 12 wks	•Double-blind • Double-dummy •Active control •Parallel-design •156 adult patients with uncontrolled epilepsy currently receiving CBZ or PHT •Protocol-specified population (n=114): all patients who completed monotherapy or met escape criteria •Intent-to-treat population (n=156): all randomized patients	•Received either LTG (500 mg/d) (n=76) or VPA 1000 mg/d (n=80) •CBZ or PHT was reduced by 20% decrements until fully withdrawn	•Primary: •Proportion of patients in each treatment group meeting escape criteria any time after concomitant AED withdrawal •Escape criteria: •Doubling of average monthly seizure rate •Doubling of the highest consecutive 2-day seizure rate •Emergence of a new, more severe seizure type •Clinically significant prolongation of generalized tonic-clonic seizures •Secondary: •Time to meeting escape crietia	•56% (LTG) vs. 20% (active control) successfully completed the study ($P < 0.001$) •37% (LTG) vs 16% (active control) completed the monotherapy period per intent-to-treat analysis ($P=0.0012$) •Significantly longer time to escape for LTG vs active control (median 168 days vs 57 days) per protocol-specified analysis ($P=0.001$) •Rates of many common adverse events reduced by ~50% following conversion to monotherapy with LTG •Most commonly reported adverse events during the monotherapy period with LTG: vomiting, headache, dizziness, nausea, dyspepsia, and coordination abnormalities •Rash occurred in 11% (n=8) of patients receiving LTG vs 8% (n= 6) receiving VPA during the initial 8-week transition period •2% (n=1) of both treatment groups experienced rash during monotherapy
lamotrigine (LTG); valproate (VPA); antiepileptic drug (AED); placebo (PBO); week (wk); kilogram (kg); phenytoin (PHT); carbamazepine (CBZ); felbamate (FBM); gabapentin (GBP); primary generalized tonic-clonic (PGTC)					

Citation	Duration	Study Design	Dosing	Endpoints	Results
Conversion To Monotherapy From Valproate In Adults With Partial Seizures					
Sale et al [9]	•Dose escalation of LTG: 8 wks •VPA withdrawal: 6 wks •Monotherapy with LTG : 4 wks	•Open-label •Pharmacokinetic study •77 adult patients with epilepsy receiving VPA and experiencing poor seizure control or unacceptable side effects •Monotherapy Completer Population: Included patients who completed the final visit (4th week) in the monotherapy phase of LTG and followed the dosing conversion algorithm as outlined in the protocol •Pharmacokinetic Population: Included patients with ≥ 1 serum concentration after initiation of LTG and followed the dosing conversion algorithm as outlined in the protocol • Intent-To-Treat Population: Included patients who received ≥1 dose of LTG	•After escalating LTG to 200 mg/d with VPA, doses of VPA were gradually decreased and doses of LTG were gradually increased up to 500 mg/d based on clinical response	•Primary: •Trough serum lamotrigine concentrations •Secondary: •Adverse events •Seizure control	•During the VPA withdrawal phase: •Mean LTG concentrations did not differ significantly from values at the end of the escalation phase of LTG in either population •During the monotherapy phase of LTG: •Mean LTG concentrations did not deviate clinically (< 10%) from values at the end of the escalation phase of LTG •Common adverse events reported with LTG included dizziness (23%), nausea (16%), headache (14%), tremor (13%), asthenia (12%) •Rash (n=5); none considered serious
lamotrigine (LTG); valproate (VPA); antiepileptic drug (AED); placebo (PBO); week (wk); kilogram (kg); phenytoin (PHT); carbamazepine (CBZ); felbamate (FBM); gabapentin (GBP); primary generalized tonic-clonic (PGTC)					

Table 41. Landmark Maintenance Trial M

Citation (reference)	Study Duration	Study Design	Dosing	Endpoints	Results
Bowden et al [10,1] *Landmark Maintenance Trial M*	**Screening phase:** 2 wks **Open-label phase:** 8-16 wks **Double-blind phase:** up to 76 wks	•Placebo-controlled •Double-blind •Randomized •Multicenter •Adult bipolar I patients (mean age 40.7 years) who were currently or recently manic or hypomanic (within 60 days) •Flexible dosing of *Lamictal*	**Open-label** (n=349): •*Lamictal* initiated as adjunctive or monotherapy and other psychotropic drugs gradually discontinued •Monotherapy (or with enzyme neutral agents) dosing titrated to response over 6 wks (target dose 200 mg/d): Wk 1-2: 25 mg/d Wk 3-4: 50 mg/d Wk 5: 100 mg/d Wk 6: 200 mg/d •Dosing adjusted for concomitant VPA and CBZ **Double-blind** (n=174): •Patients from open-label phase who reached stabilization criteria (CGI-severity score of ≤3 and maintained for ≥4 continuous weeks, including at least the final week on monotherapy with *Lamictal*)	**Primary endpoint:** •Time to intervention [addition of pharmacotherapy or ECT for a bipolar I episode or one that was emerging (TIME)] **Secondary endpoints:** •Time to early discontinuation for any reason (ie, survival in study) •Time to intervention for a manic, hypomanic, or mixed episode•Time to intervention for a depressive episode •Mean change from baseline (defined as Day 1 of the double-blind phase)	**Primary endpoint:** •Compared with PBO, *Lamictal* was significantly superior at prolonging TIME ($P = 0.018$) **Secondary endpoints:** •*Lamictal* was also superior to PBO in overall survival in study ($P = 0.03$) •*Lamictal* was superior to PBO at prolonging time to a depressive episode ($P = 0.015$) but not manic or hypomanic episodes ($P = 0.280$) •At 76 wks, an estimated 83% of patients taking *Lamictal* were intervention-free for a depressive episode compared to 40% on PBO (as extrapolated from the Kaplan-Meier Survival curve) Most common adverse events reported by patients taking *Lamictal* vs PBO during double-blind phase: • Headache (20% vs 16%) • Infection (14% vs 14%) • Influenza (10% vs 6%) • Somnolence (8% vs 9%) • Insomnia (8% vs 6%) • Nausea (7% vs 9%) • Diarrhea (5% vs 9%) • Any rash (3% vs 9%)
			entered 18-month double-blind maintenance phase and received *Lamictal* (100 - 400 mg/d based on clinical response at randomization), lithium (0.8 – 1.1 mEq/L) or PBO as maintenance monotherapy •Mean dose of *Lamictal* 211 mg/d	on the MRS, HAM-D, CGI, and GAS scores during double-blind treatment •Adverse events	

* Note: Lithium was used as an active control in these pivotal trials. Therefore, results of lithium effect are not reflected in approved product labeling for *Lamictal* and are not represented in this section

wks (weeks); d (day); VPA (valproate); CBZ (carbamazepine); CGI (Clinical Global Impressions); PBO (placebo); ECT (electroconvulsive therapy); MRS (Mania Rating Scale); HAM-D (Hamilton Rating Scale for Depression); GAS (Global Assessment Scale)

Table 42. Landmark Maintenance Trial D

Citation (reference)	Study Duration	Study Design	Dosing	Endpoints	Results
Calabrese et al [11,1] *Landmark Maintenance Trial D*	**Screening phase:** 2 wks **Open-label phase:** 8-16 wks **Double-blind phase:** up to 76 wks	•Placebo-controlled •Double-blind •Randomized •Multicenter •Adult bipolar I patients (mean age 42.2 years) who were currently or recently depressed (within 60 days) •Fixed dose of *Lamictal*	**Open-label** (n=966): •Same as Bowden et al [10] **Double-blind** (n=463): •Patients from open-label phase who reached stabilization criteria (CGI-severity score of ≤ 3 and maintained for ≥ 4 continuous weeks, including at least the final week on monotherapy with *Lamictal*) entered an 18-month double-blind maintenance phase and received *Lamictal* (3 fixed dose groups, 50 mg/d, 200 mg/d, or 400 mg/d),* lithium, or PBO as maintenance monotherapy ** 50-mg and 400-mg groups were discontinued to facilitate enrollment. 200-mg and 400-mg groups were prospectively combined for analysis of efficacy.*	**Primary endpoint:** •Time to intervention **Secondary endpoints:** •Time to early discontinuation for any reason •Time to intervention for a manic, hypomanic, or mixed episode •Time to intervention for a depressive episode •Mean change from baseline (defined as Day 1 of the double-blind phase) on the MRS, HAM-D, CGI, and GAS scores during double-blind treatment •Adverse events	**Primary endpoint:** •Compared with PBO, *Lamictal* was significantly superior at prolonging TIME ($P = 0.029$) **Secondary endpoints:** •*Lamictal* superior to PBO on overall survival in study ($P = 0.003$) •*Lamictal* superior to PBO at prolonging depressive episodes ($P = 0.047$), but not for manic and hypomanic episodes ($P = 0.339$) Most common adverse events reported by patients taking *Lamictal* vs PBO during double-blind phase: • Headache (18% vs 21%) • Nausea (17% vs 12%) • Infection (12% vs 12%) • Insomnia (10% vs 7%) • Somnolence (9% vs 6%) • Dizziness (8% vs 10%) • Influenza (8% vs 11%) • Diarrhea (7% vs 8%) • Any rash (7% vs 2%) • Tremor (5% vs 5%) • n=1 serious rash in open-label phase and none during double-blind phase

** Note: Lithium was used as an active control in these pivotal trials. Therefore, results of lithium effect are not reflected in approved product labeling for Lamictal and are not represented in this section*

wks (weeks); d (day); CGI (Clinical Global Impressions); PBO (placebo); MRS (Mania Rating Scale); HAM-D (Hamilton Rating Scale for Depression); GAS (Global Assessment Scale)

Table 43. Combined Analysis of Landmark Maintenance Trials M & D

Citation (reference)	Study Duration	Study Design	Dosing	Endpoints	Results
Goodwin et al [12,1] *Combined Analysis of Landmark Maintenance Trials M & D*	**Screening phase:** 2 wks **Open-label phase:** 8-16 wks **Double-blind phase:** up to 76 wks	•Placebo-controlled •Double-blind •Randomized •Multicenter •Adult bipolar I patients (mean age 42 years) who were currently or recently manic, hypomanic, or depressed (within 60 days) •Prospectively combined analysis of Bowden et al [10] and Calabrese et al [11]	Refer to Bowden et al,[10] Calabrese et al[11] for detailed dosing information • Open-label (n=1305) • Double-blind (n=638) • Mean dose of *Lamictal* 245 mg/d	**Primary endpoint:** •Time to intervention **Secondary endpoints:** •Time to early discontinuation for any reason •Time to intervention for a manic, hypomanic, or mixed episode •Time to intervention for a depressive episode •Mean change from baseline (defined as Day 1 of the double-blind phase) on the MRS, HAM-D, CGI, and GAS scores during double-blind treatment • Adverse events	**Primary endpoint:** •*Lamictal* was superior to PBO at prolonging TIME ($P < 0.001$) **Secondary endpoints:** •*Lamictal* was superior to PBO in delaying the time to occurrence of both depression and mania, although the finding was more robust for depression •*Lamictal* was superior to PBO in: •Prolonging time to intervention for a depressive episode (P=0.009) •Prolonging time to intervention for a manic episode (P=0.034) •Prolonging overall survival in the study ($P < 0.001$) •Lowering HAMD-17 mean scores during randomized phase ($P = 0.027$)

** Note: Lithium was used as an active control in these pivotal trials. Therefore, results of lithium effect are not reflected in approved product labeling for Lamictal and are not represented in this section*

wks (weeks); d (day); CGI (Clinical Global Impressions); PBO (placebo); MRS (Mania Rating Scale); HAM-D (Hamilton Rating Scale for Depression); GAS (Global Assessment Scale)

Citation (reference)	Study Duration	Study Design	Dosing	Endpoints	Results
					Most common adverse events reported by patients taking *Lamictal* vs PBO during double-blind phase: • Headache (19% vs 19%) • Nausea (14% vs 11%) • Infection (13% vs 13%) • Any rash (7% vs 5%) • Dizziness (7% vs 9%) • Somnolence (9% vs 7%) • Diarrhea (7% vs 8%) • Insomnia (10%vs 6%) • Tremor (4% vs 5%) • n=2 serious rashes reported in open-label phase and none in double-blind phase •Discontinuation rates due to AEs: 13% for *Lamictal*, 23% for lithium, 16% for PBO
** Note: Lithium was used as an active control in these pivotal trials. Therefore, results of lithium effect are not reflected in approved product labeling for Lamictal and are not represented in this section* wks (weeks); d (day); CGI (Clinical Global Impressions); PBO (placebo); MRS (Mania Rating Scale); HAM-D (Hamilton Rating Scale for Depression); GAS (Global Assessment Scale)					